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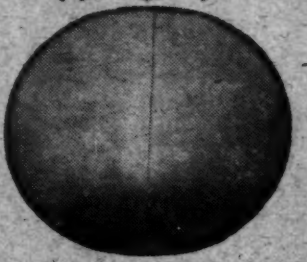

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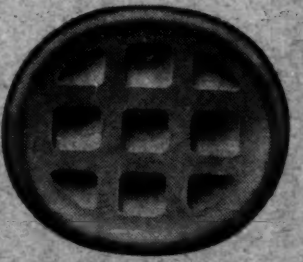

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BRITISH MEDICAL JOURNAL

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ANTIRHEUMATIC EFFECTS OF HYDROCORTISONE (FREE ALCOHOL), HYDROCORTISONE ACETATE, AND CORTISONE (FREE ALCOHOL) AS COMPARED WITH CORTISONE ACETATE

RESULTS FROM ORAL ADMINISTRATION IN PATIENTS WITH RHEUMATOID ARTHRITIS

BY

EDWARD W. BOLAND, M.D., M.S.Med., F.A.C.P.

Los Angeles, California

The results of prolonged uninterrupted cortisone acetate therapy given orally to patients with rheumatoid arthritis were recently reported.[1] By using initial suppressive amounts of the hormone, then gradually reducing the dosage in step-like manner, and finally employing smaller maintenance doses, it was possible to sustain satisfactory, though not complete, rheumatic control in approximately two-thirds of the patients. Adequate degrees of improvement were maintained in 47% of severe cases, in 70% of moderately severe cases, and in 92% of moderate and mild cases. Results were poorer in those patients whose disease was severe, because they required continued large or relatively large maintenance amounts of the hormone which often could not be tolerated, as they incited objectionable hormonal complications; large but efficient doses frequently had to be reduced, with sacrifice to clinical improvement.

The limitations of cortisone acetate as a therapeutic agent, together with its cost, and, until recently, its restricted supply, have led investigators to search for steroidal substitutes which might possess similar anti-inflammatory and anti-allergic properties. Many substances, some closely allied chemically to cortisone, have been tested by critical observers and have been found devoid of significant antirheumatic activity in the dosage ranges explored. Among these may be listed: substance S of Reichstein (11-desoxycorticosterone),[2 3] compound A of Kendall (11-dehydrocorticosterone),[4 5] 21-desoxycortisone,[5] 21-desoxy-11-dehydrocorticosterone,[5] desoxycorticosterone acetate (alone or with ascorbic acid),[6 7 8 9 10] 17-hydroxyprogesterone,[11 12] pregnenethiolone acetate,[3 7] delta-5-pregnenolone,[5 12 13] and 21-acetoxypregnenolone.[2 5 12] An exception has been Kendall's compound F (17-hydroxycorticosterone: "substance M" of Reichstein), recently named "hydrocortisone," which has shown physiological activity at least comparable to that of cortisone. Weak antirheumatic action has been demonstrated also by certain adrenal cortical extracts, their strength apparently depending upon the amounts of cortisone or hydrocortisone they contain.[5]

In April, 1951, small quantities of hydrocortisone acetate were made available to us, and two patients with rheumatoid arthritis were given the drug orally. The doses needed to suppress the rheumatic manifestations were substantially greater than those ordinarily required for cortisone acetate.[14] Conversely, pilot trials made later with hydrocortisone (free alcohol) indicated that this substance was highly effective and perhaps even more potent than cortisone acetate. Subsequently, when supplies of materials permitted, a systematic study designed to compare the antirheumatic potencies of cortisone acetate, hydrocortisone (free alcohol), hydrocortisone acetate, and cortisone (free alcohol) was undertaken. Appraisals of the relative clinical effectiveness of these compounds were made by: (1) estimating differences in initial clinical response to large suppressive doses, and (2) comparing the maintenance doses required to uphold equivalent degrees of clinical improvement in the same patient. The results of this investigation are reported here.

In comparing the maintenance-dosage requirements of other compounds with those already established for cortisone acetate, care was taken to select only those patients whose maintenance doses of cortisone acetate had remained quite stable over periods of weeks or months. Transfers from one substance to another were not made in rapid sequence and patients were usually kept on the test preparation for at least two or three weeks. They were then transferred back to the original compound in order to cross-check differences. During the study attempts were made to compare the amounts of the compounds needed to sustain marked (70 to 85%) improvement, but not complete suppression of the disease. Thus sufficient subjective and objective manifestations remained to allow changes in rheumatic response to be measured.

Cortisone Acetate

The favourable influence of cortisone acetate therapy on rheumatoid arthritis has been repeatedly documented. In more than 150 patients treated with the compound by oral administration we have followed a fairly uniform plan of dosage, which has consisted of three stages: (1) a period of initial suppressive doses; (2) a period of gradual dose reduction; and (3) a period of smaller maintenance-dose administration.[1 15 16 17]

Initial suppressive therapy usually has been given as follows: for severe and moderately severe cases, 200 or 150 mg. for the first one or two days, followed by 100 mg.

daily; for moderate and mild cases, 100 mg. on the first and subsequent days. The drug has been prescribed in four divided doses daily, at meal-times and at bedtime. Amounts of 100 mg. have been continued until the clinical manifestations were suppressed satisfactorily; the number of days required for this has varied, more or less, with the initial activity of the disease, averaging, for example, about 21 days for severe cases and about 14 days for moderate cases. The dosage then has been gradually reduced in steplike fashion, by 12.5 mg. (half a tablet) at a time at intervals of every five to seven days. The smallest daily amount which would sustain adequate suppression of rheumatic symptoms, not necessarily full symptomatic relief, has been regarded as the patient's maintenance dose. This dose has been continued uninterruptedly, adjustments being made from time to time to counteract fluctuations in disease activity.

With large suppressive amounts of cortisone acetate given by mouth, symptoms generally begin to subside within the first 24 hours of treatment, and almost invariably some response is noted within the first 48 hours. Early benefits consist in reduction of aching and stiffness, lessening of articular tenderness and pain, increase in range of joint motion, lessening of fatigue, and increased appetite. Joint swelling and other reversible objective changes recede more gradually, but with continued administration the overall improvement progresses. Elevated erythrocyte sedimentation rates are corrected more slowly than are the joint manifestations, and their reductions usually lag several days behind clinical improvement. In spite of continued large daily doses of the hormone, however, sedimentation rates may at times fail to decrease to levels commensurate with the rheumatic response.

After the manifestations have been brought under initial control and the dose has been gradually reduced, the daily amount of cortisone acetate needed to maintain satisfactory symptomatic suppression varies, but it depends to a large extent on the initial activity of the rheumatoid arthritis—the more severe the disease, the more cortisone acetate required. Usual ranges for maintenance doses have been: 62.5 to 125 mg. a day for severe cases; 50 to 75 mg. a day for moderately severe cases; 37.5 to 62.5 mg. for moderate cases; and 25 to 50 mg. a day for mild cases. In nearly two-thirds of patients the dosage has remained fairly constant for months, with only minor adjustments being needed periodically. In about one-third of patients the amounts of hormone required have fluctuated considerably from time to time, and major manipulations of dosage have been necessary to offset changes in disease activity.

Hydrocortisone (Free Alcohol)

Hydrocortisone (Kendall's compound F, free alcohol: 17-hydroxycorticosterone) differs from cortisone (Kendall's compound E, free alcohol: 17-hydroxy-11-dehydrocorticosterone) in that a hydroxy radical instead of a ketone group is present at the eleventh carbon position of the steroid nucleus. From facts now available it seems probable that hydrocortisone rather than cortisone is the chief glycogenically active corticoid secreted by the adrenal gland, at least under conditions of stress.[18 19] A number of laboratory procedures indicate that hydrocortisone is more active physiologically than cortisone. Comparisons made from muscle-work tests, assays of liver glycogen, and ability to incite regressive changes in the thymus and adrenals have shown that when the non-esterified forms of the two hormones are given intravenously or subcutaneously hydrocortisone is approximately twice as potent as cortisone.[20 21 22 23] It also appears that one-half as much hydrocortisone as cortisone will promote an equivalent eosinopenic response.[24]

Meagre quantities of hydrocortisone (free alcohol) have been available for laboratory and clinical research because production of the hormone has depended upon complicated processes of biosynthesis. These have involved the transformation of 11-desoxy-17-hydrocorticosterone (Reichstein's compound S)—a steroid which may be derived from soy beans and which is devoid of anti-inflammatory activity—to hydrocortisone through the action of adrenal cortical enzymes. By enriching the substrate with 11-desoxy-17-hydrocorticosterone and perfusing it through intact isolated bovine adrenal glands or by adding it to and incubating it with slices of adrenal cortex, this steroid is converted (by placing a hydroxy radical at the eleventh carbon atom) to hydrocortisone. Very recently small amounts of the hormone produced by partial chemical synthesis have been made available for trial.

In 1949 Hench and colleagues demonstrated that hydrocortisone (free alcohol), like cortisone and corticotropin (A.C.T.H.), possessed antirheumatic activity when administered systemically.[4 25 26] They gave a total of 900 mg. of the hormone intramuscularly to one patient with rheumatoid arthritis over a 12-day period and noted that the articular manifestations subsided rapidly; overall relief was estimated as 60% and the erythrocyte sedimentation rate was reduced from 85 to 24 mm. in one hour. No other accounts of the effects of hydrocortisone (free alcohol) given systemically to patients with rheumatoid arthritis have been recorded.

Experience with Suppressive Doses of Hydrocortisone (Free Alcohol) Given Orally

Five patients with rheumatoid arthritis of the peripheral type who had not previously received hormonal therapy for arthritis were given large initial doses of hydrocortisone (free alcohol) by mouth.* The disease was graded as severe in one patient, moderately severe in three, and moderate in one; erythrocyte sedimentation rates before treatment were 119, 61, 60, 53, and 48 mm. in one hour (Westergren method) in the respective patients. Four of the subjects were women and one was a man. Their ages ranged from 42 to 56 years.

The one patient with severe disease received 150 mg. of the hormone daily for two days and then 100 mg. each day for 13 days. The three patients with moderately severe and the one patient with moderate rheumatoid arthritis received 100 mg. on the first day and for several days thereafter. Because supplies of hydrocortisone were limited, the doses given on the first day of treatment were smaller than those customarily employed for cortisone acetate in cases of similar severity.

The results from suppressive doses of hydrocortisone (free alcohol) will be reported elsewhere in greater detail.[27] The initial response was strikingly prompt in each patient, and symptoms such as aching and stiffness began to subside within three, four, six, seven, and ten hours respectively after the first dose of the hormone. In four patients (three with moderately severe and one with moderate rheumatoid arthritis) subsequent progress was extremely rapid, and very marked degrees of overall improvement (more than 85%), as gauged by both objective and subjective criteria, resulted after four, six, six, and eight days. In these the improvement progressed at a more rapid rate and was more complete than that which usually follows oral cortisone acetate therapy within such periods, even when larger doses are given on the first day. The fifth patient (with severe disease) responded less dramatically, and the improvement was graded as marked after 15 days; the rate of improvement was considered to be about the same as might have resulted from cortisone acetate given in identical doses.

Erythrocyte sedimentation rates were lowered with remarkable speed and, in contrast to the lag which is often noted during cortisone acetate therapy, reductions kept pace closely behind clinical improvement. Elevated rates in the five patients were reduced as follows: 53 to 10 mm. in 7 days, 60 to 20 mm. in 7 days, 61 to 11 mm. in 10 days, 48 to 16 mm. in 6 days, and 119 to 39 mm. in 15 days.

*Gratitude is expressed to G. D. Searle & Co., who supplied most of the hydrocortisone (free alcohol); to Merck & Co., Inc., who supplied the cortisone acetate; and to the Upjohn Company, who supplied part of the hydrocortisone (free alcohol).

Comparisons of Maintenance-dosage Requirements of Cortisone Acetate and Hydrocortisone (Free Alcohol)

By directly comparing the maintenance doses required in the same patient to provide similar antirheumatic control, appraisals of the relative potencies of cortisone acetate and hydrocortisone (free alcohol) could be made more accurately than by estimating differences in the immediate response to suppressive doses. Ten patients with rheumatoid arthritis who had been treated uninterruptedly with cortisone acetate orally for long periods (3 to 16 months), and whose maintenance requirements were stable and well established, were transferred directly to hydrocortisone (free alcohol). Uniformly the patients needed smaller amounts of hydrocortisone (free alcohol) for equivalent degrees of clinical improvement. Dosage differences were clearly defined and, milligram for milligram, hydrocortisone (free alcohol) was found to be approximately 50% more potent than cortisone acetate. Dosage ratios of cortisone acetate to hydrocortisone (free alcohol) ranged from 1.43:1 to 1.7:1 among the ten patients, and the average ratio for the group was 1.56:1 (Table I).

In three of the five patients the initial response was definitely less than would ordinarily be experienced with corresponding large suppressive doses of cortisone acetate, but in two patients (both with moderately severe disease) the progress of improvement was similar. In the five patients some degree of symptomatic relief was noted within 8, 15, 24, 24, and 30 hours after the first dose of hydrocortisone acetate, but in three of them the immediate reaction was not striking, and at the end of several days of treatment the overall improvement was considered to be distinctly less than should have resulted from similar amounts of cortisone acetate.

Response to suppressive therapy varied among the five patients as follows. The first patient, with moderately severe rheumatoid arthritis, exhibited moderate symptomatic relief after the first day's treatment with 200 mg. of hydrocortisone acetate, and after 48 hours some improvement in the objective joint findings was recorded. Two days after the dose was reduced to 100 mg. a day, however, regression ensued and very little additional improvement resulted from continued administration. After 15 days, improvement was graded as slight (less than 30%) and the erythrocyte sedimentation rate had not changed significantly (58 to 56 mm. in one hour). The dose of hydrocortisone acetate was then raised to 200 mg. a day for 10 days; further suppression of the disease manifestations promptly ensued, but endocrine side-reactions, consisting of pronounced mooning of the face, nervousness, insomnia, and oedema of the lower legs, also developed.

TABLE I.—*Maintenance-dosage Requirements for Cortisone Acetate and Hydrocortisone (Free Alcohol) Given Orally in Rheumatoid Arthritis*

Case	Severity of Disease	Degree of Overall Improvement	Maintenance Doses needed for Equivalent Degrees of Clinical Improvement						Average Dosage Ratios Cortisone Acetate to Hydrocortisone (Free Alcohol)
			First Comparison		Second Comparison		Averages		
			Cortisone Acetate (mg.)	Hydrocortisone (Free Alcohol) (mg.)	Cortisone Acetate (mg.)	Hydrocortisone (Free Alcohol) (mg.)	Cortisone Acetate (mg.)	Hydrocortisone (Free Alcohol) (mg.)	
1	Mod. severe	Marked (85%)	62·5	40	62·5	50	62·5	40·0	1·56 to 1
2	,, ,,	,, (85%)	62·5	40	62·5	40	62·5	40·0	1·56 ,, 1
3	,, ,,	,, (75%)	75·0	50	75·0	55	75·0	52·5	1·43 ,, 1
4	,, ,,	,, (85%)	62·5	40	—	—	62·5	40·0	1·56 ,, 1
5	Severe	,, (75%)	75·0	50	75·0	50	75·0	50·0	1·50 ,, 1
6	,,	,, (80%)	125·0	80	125·0	70	125·0	75·0	1·67 ,, 1
7	,,	,, (75%)	68·8	40	62·5	40	65·7	40·0	1·64 ,, 1
8	Mod. severe	,, (85%)	62·5	40	—	—	62·5	40·0	1·56 ,, 1
9	,, ,,	,, (85%)	62·5	40	75·0	40	68·8	40·0	1·72 ,, 1
10	Mod.	Very marked (90%)	50·0	35	—	—	50·0	35·0	1·43 ,, 1
								Average	1·56 ,, 1

Hydrocortisone Acetate

Hydrocortisone acetate (17-hydroxycorticosterone-21-acetate: compound F acetate) is produced by partial chemical synthesis from desoxycholic acid, through a similar but more complex process than that used in the manufacture of cortisone acetate. Reports of systemic administration of this compound to patients with rheumatoid arthritis have been few. Perera and associates[9] gave the drug intramuscularly to two patients with the disease; one received 100 mg. a day for 24 days and the other 12.5 mg. a day for 11 days. They concluded that the clinical and metabolic effects may have been somewhat less than would have occurred with cortisone acetate. Ward and co-workers[10] judged that the improvement which resulted in two patients who received the compound orally was comparable to that expected from cortisone acetate in corresponding doses.

Experience with Suppressive Doses of Hydrocortisone Acetate*

The acetate ester of hydrocortisone was administered orally as initial treatment to five women, one with severe and four with moderately severe rheumatoid arthritis. Erythrocyte sedimentation rates before treatment were recorded as 103, 67, 58, 53, and 50 mm. in one hour (Westergren method). Dosages used were identical to those customarily employed with cortisone acetate in cases of like severity: 200 mg. in divided doses was given on the first and second days of treatment and 100 mg. daily thereafter to the patient with severe arthritis; 200 mg. was administered on the first day and 100 mg. on subsequent days to the four patients with moderately severe disease.

After 19 days of treatment overall improvement was estimated as between 20 and 30% and the sedimentation rate had not decreased greatly, from 103 to 87 mm. in one hour. The preparation was then given in amounts of 150 mg. a day for a period of nine days; this afforded somewhat greater relief, and improvement was finally graded as moderate (about 50%). At this point transfer to cortisone acetate in amounts of 100 mg. a day was accomplished. Within 18 hours there was striking acceleration of improvement, and continued administration resulted in rapid sup-

The second patient suffered from severe rheumatoid arthritis, and previously, for a period of 11 months, she had responded well to uninterrupted cortisone acetate administration. The immediate improvement from cortisone acetate had been dramatic, and satisfactory control was held with daily amounts ranging from 50 to 75 mg. Cortisone acetate therapy had been discontinued five months beforehand in order to ascertain the rate of return of adrenal cortical function following long-term therapy; functional recovery, as indicated by the eosinopenic response to corticotropin and urinary 17-ketosteroid determinations, had returned to normal within 45 days after withdrawal. The improvement resulting from hydrocortisone acetate in amounts of 200 mg. daily for two days and then 100 mg. a day was graded as slight.

*The hydrocortisone acetate used in this investigation was supplied by Merck & Co., Inc.

TABLE II.—*Maintenance Requirements for Cortisone Acetate and Hydrocortisone Acetate Given Orally in Rheumatoid Arthritis*

Case	Severity of Disease	Degree of Overall Improvement	Maintenance Doses needed for Equivalent Degrees of Clinical Improvement						Average Dosage Ratios Cortisone Acetate to Hydrocortisone Acetate
			First Comparison		Second Comparison		Averages		
			Cortisone Acetate (mg.)	Hydrocortisone Acetate (mg.)	Cortisone Acetate (mg.)	Hydrocortisone Acetate (mg.)	Cortisone Acetate (mg.)	Hydrocortisone Acetate (mg.)	
1	Mod. severe	Marked (85%)	62·5	87·5	—	—	62·5	87·5	1 to 1·40
2	Severe	,, (75%)	62·5	100·0	62·5	75·0	62·5	87·5	1 ,, 1·40
3	Mod. severe	,, (85%)	50·0	75·0	62·5	100·0	56·3	87·5	1 ,, 1·55
4	,, ,,	,, (85%)	62·5	87·5	62·5	100·0	62·5	93·8	1 ,, 1·50
5	,, ,,	,, (85%)	62·5	87·5	62·5	75·0	62·5	81·3	1 ,, 1·30
6	,, ,,	,, (75%)	75·0	100·0	—	—	75·0	100·0	1 ,, 1·33
7	,, ,,	,, (85%)	62·5	62·5	62·5	62·5	62·5	62·5	1 ,, 1·00
8	Severe	,, (75%)	75·0	125·0	62·5	100·0	68·8	112·5	1 ,, 1·64
9	Mod.	,, (80%)	50·0	75·0	50·0	50·0	50·0	62·5	1 ,, 1·25
								Average	1 ,, 1·37

pression of the rheumatic manifestations, comparable to that which had been experienced from previous treatment with cortisone acetate.

The third patient, with moderately severe disease, experienced rapid and progressive improvement from suppressive doses of hydrocortisone acetate, which at the end of 16 days was graded as marked (80%). Thereafter the dosage was gradually reduced to a maintenance level of 62.5 mg. a day, which was sufficient to uphold satisfactory suppression of the clinical manifestations. The erythrocyte sedimentation rate failed to reflect the good rheumatic response, however, and at the end of 22 days of treatment had decreased only from 67 to 46 mm. in one hour. Transfer to cortisone acetate was subsequently made, and the same maintenance dose was required to provide equivalent clinical control.

The fourth patient, with moderately severe rheumatoid arthritis, responded slowly and undramatically to initial suppressive doses of hydrocortisone acetate, and after 20 days of treatment the overall improvement was graded as moderate or about 50%. The erythrocyte sedimentation rate decreased during the period from 53 to 40 mm. in one hour.

The fifth patient, with moderately severe disease, responded well to 200 mg. of hydrocortisone acetate on the first day, noting subjective improvement within 24 hours after the initial divided dose. Subsequent progress on total daily amounts of 100 mg. was steady, and after 19 days of treatment the improvement was graded as marked (about 80%). The erythrocyte sedimentation rate during this period was reduced from 50 to 20 mm. in one hour.

Comparisons of Maintenance-dosage Requirements of Cortisone Acetate and Hydrocortisone Acetate

In contrast to hydrocortisone (free alcohol), which was found to be more potent than cortisone acetate when the maintenance requirements of the two substances were tested on the same patients, hydrocortisone acetate was less effective, milligram for milligram, than cortisone acetate in eight of nine patients studied. Dosage ratios of cortisone acetate to hydrocortisone acetate ranged from 1:1 to 1.64:1 among the nine patients, with an average for the group of 1.37:1 (Table II).

Comparisons of Maintenance-dosage Requirements of Hydrocortisone (Free Alcohol) and Hydrocortisone Acetate

Direct comparisons of these two compounds in the same patients clearly demonstrated that hydrocortisone (free alcohol) was distinctly superior to hydrocortisone acetate in controlling the manifestations of rheumatoid arthritis. Results were fairly uniform in nine patients tested, and indicated that hydrocortisone (free alcohol) was nearly twice as potent, milligram for milligram, when the two substances were given by mouth (Table III).

TABLE III.—*Maintenance Requirements for Hydrocortisone (Free Alcohol) and Hydrocortisone Acetate Given Orally in Rheumatoid Arthritis*

Case	Severity of Disease	Degree of Overall Improvement	Maintenance Doses Needed for Equivalent Degrees of Clinical Improvement		Average Dosage Ratios: Hydrocortisone (Free Alcohol) to Hydrocortisone Acetate
			Hydrocortisone (Free Alcohol) (mg.)	Hydrocortisone Acetate (mg.)	
1	Severe	Marked (75%)	40	87·5	1 to 2·19
2	Mod. severe	,, (80%)	40	75·0	1 ,, 1·88
3	,, ,,	,, (80%)	60	125·0	1 ,, 2·08
4	,, ,,	,, (80%)	40	75·0	1 ,, 1·88
5	,, ,,	,, (75%)	50	100·0	1 ,, 2·00
6	,, ,,	,, (80%)	40	87·5	1 ,, 2·19
7	Severe	,, (75%)	50	87·5	1 ,, 1·75
8	Mod. severe	,, (80%)	40	75·0	1 ,, 1·88
9	Mod.	,, (80%)	40	75·0	1 ,, 1·88
				Average	1 ,, 1·97

Cortisone (Free Alcohol)

Of the 21 rheumatoid arthritis patients with whom Hench, Kendall, Slocumb, and Polley[25 26] originally demonstrated that cortisone exerted an inhibiting influence on the disease, 9 received the free hormone and 12 were given the acetate ester as initial treatment. The relative therapeutic potencies of the two preparations were not compared directly by them.

When our studies revealed that hydrocortisone (free alcohol) was distinctly superior in antirheumatic activity to hydrocortisone acetate when they were administered orally, the question arose whether a similar discrepancy might exist between the free and acetated forms of cortisone. Cortisone (free alcohol)* was made available to us in small quantities, and maintenance-dosage requirements for the hormone were compared with those for cortisone acetate in seven patients, and with those for hydrocortisone (free alcohol) in six patients. The data evolved from these comparisons are given in Table IV. Supplies were not sufficient to test the effects of initial suppressive doses in previously untreated patients.

Cortisone (free alcohol) and cortisone acetate were found to be approximately equal in their antirheumatic potencies when administered by mouth. Except for minor variations in three of the seven patients, the maintenance dosages required for the two compounds were interchangeable.

Hydrocortisone (free alcohol) proved to be more effective, milligram for milligram, than cortisone (free alcohol). Although dosage differences among the individual patients showed less uniformity, the average calculated dosage ratio was much the same as with cortisone acetate. The dosage ratio of cortisone (free alcohol) to hydrocortisone (free alcohol) ranged in the six patients from 1.25 : 1 to 2.08 : 1, with an average ratio for the group of 1.6 : 1—against 1.56 : 1 for cortisone acetate to hydrocortisone (free alcohol).

*The cortisone (free alcohol) used in this investigation, produced by partial chemical synthesis, was supplied by the Upjohn Company.

TABLE IV.—*Maintenance Requirements for Cortisone (Free Alcohol), Cortisone Acetate, and Hydrocortisone (Free Alcohol) Given Orally in Rheumatoid Arthritis*

Case	Severity of Disease	Degree of Overall Improvement	Maintenance Doses Needed for Equivalent Degrees of Clinical Improvement				Calculated Dosage Ratios.	
			Cortisone Acetate (mg.)	Cortisone (Free Alcohol) (mg.)	Hydrocortisone (Free Alcohol) (mg.)	Cortisone (Free Alcohol) (mg.)	Cortisone Acetate to Cortisone (Free Alcohol)	Cortisone (Free Alcohol) to Hydrocortisone (Free Alcohol)
1	Mod. severe	Marked	62·5	62·5	40	62·5	1·0 to 1·0	1·56 to 1
2	" "	"	62·5	62·5	40	62·5	1·0 " 1·0	1·56 " 1
3	" "	"	62·5	62·5	30	62·5	1·0 " 1·0	2·08 " 1
4	" "	"	62·5	50·0	40	50·0	1·0 " 0·8	1·25 " 1
5	" "	"	62·5	75·0	40	75·0	1·0 " 1·2	1·88 " 1
6	" "	"	75·0	62·5	50	62·5	1·0 " 0·83	1·25 " 1
7	Mod.	"	50·0	50·0	—	—	1·0 " 1·0	—
						Averages	1·0 " 0·98	1·6 to 1

Comment

Data derived from the present study indicate that when administered orally hydrocortisone (free alcohol) is, milligram for milligram, approximately 50% more potent than either cortisone acetate or cortisone (free alcohol), and nearly twice as effective as hydrocortisone acetate. These observations suggest that hydrocortisone (free alcohol) may prove to be superior to cortisone acetate as a therapeutic agent. Although the hormone used in the present study was produced by expensive and complicated procedures of biosynthesis, it has been made recently by partial chemical synthesis from a precursor of cortisone. If future investigations prove that the hormone has distinct therapeutic advantages, it is probable that practical methods for its commercial manufacture will be found.

The number of cases studied were too few and the periods of observation were too short to allow the incidence of the adverse hormonal effects from hydrocortisone (free alcohol), hydrocortisone acetate, or cortisone (free alcohol) to be compared with those already known for cortisone acetate. However, it seems that the greater antirheumatic activity of hydrocortisone (free alcohol) is not accompanied by a correspondingly greater tendency to produce adverse reactions. Endocrine complications were present in several patients during the administration of maintenance doses of cortisone acetate, and these disappeared or diminished when the patients were transferred to smaller but equally effective amounts of hydrocortisone (free alcohol). Five of the ten patients transferred from cortisone acetate to hydrocortisone (free alcohol) had signs of hormonal excess prior to transfer. Slight to moderate oedema, which was present beforehand in four patients, disappeared entirely after hydrocortisone (free alcohol) therapy was instituted. Facial mooning, which was present in two patients, became less noticeable in one and receded completely in the other. In no patient did new hormonal complications develop after transfer to hydrocortisone (free alcohol). We believe that this lessening of adverse effects may be accounted for by the fact that smaller doses of hydrocortisone (free alcohol) were employed to control the rheumatoid arthritis.

The reasons for the marked disparity in therapeutic effectiveness between hydrocortisone (free alcohol) and hydrocortisone acetate when administered orally are not entirely clear, but the relatively low solubility of hydrocortisone acetate may provide at least part of the explanation. Recent studies made at the Merck Laboratories have demonstrated that hydrocortisone (free alcohol), when compared with hydrocortisone acetate, is approximately 28 times more soluble in water, six times more soluble in synovial fluid, 35 times more soluble in plasma, and 36 times more soluble in serum albumin.[30] The lower solubility of hydrocortisone acetate could substantially lessen the rate and degree of its alimentary absorption.

Recently Hollander and co-workers,[31,32] and others[33,34] have observed that intra-articular injections of small quantities (25 to 50 mg.) of hydrocortisone acetate are highly effective in temporarily suppressing the inflammatory reaction in individual joints treated, but that similar injections of cortisone acetate are not so successful. These findings are in contrast to our results from oral administration, in which cortisone acetate exhibited the greater potency. Again this could be explained, but possibly only in part, on the basis of differences in solubility and absorption of the two compounds. Solubility data have revealed that cortisone acetate is approximately twice as soluble in water as hydrocortisone acetate, nine times as soluble in synovial fluid, eight times as soluble in plasma, and 18 times as soluble in serum albumin.[30] Whereas the low solubility of hydrocortisone acetate may lessen its therapeutic effectiveness with oral administration, it may, by delaying absorption from the joint and allowing more prolonged local action, serve as an advantage with intra-articular application.

Summary

Comparisons of the antirheumatic effects of hydrocortisone (free alcohol), hydrocortisone acetate, cortisone (free alcohol), and cortisone acetate given orally for short periods were made in patients with rheumatoid arthritis. The relative potencies of the preparations were appraised by estimating the differences in clinical response to initial suppressive doses, and by comparing directly in the same patient the maintenance doses required to uphold similar degrees of clinical improvement.

Hydrocortisone (free alcohol) was found to possess greater antirheumatic activity, milligram for milligram, than any of the other three preparations when given by mouth. This substance, administered in large initial doses, was highly efficient in suppressing the disease manifestations of rheumatoid arthritis, and its action appeared to be more rapid than that regularly encountered with cortisone acetate. By comparing the maintenance doses required for equivalent clinical control, hydrocortisone (free alcohol) was found to be approximately 50% more potent than either cortisone (free alcohol) or cortisone acetate, and nearly twice as effective as hydrocortisone acetate.

In a small number of patients tested by comparing maintenance-dosage requirements the effectiveness of cortisone (free alcohol) and cortisone acetate appeared to be about equal.

The relative incidence of endocrine complications from the various preparations could not be determined from the short-term studies involved. However, the greater antirheumatic activity of hydrocortisone (free alcohol) did not seem to be accompanied by a correspondingly greater tendency to produce adverse physiological effects. In several patients signs of hormonal excess present while on maintenance doses of cortisone acetate actually diminished or disappeared after transfers were made to smaller, but equally effective, doses of hydrocortisone (free alcohol).

The marked disparity in therapeutic effectiveness between hydrocortisone (free alcohol) and hydrocortisone acetate when given by mouth may be accounted for, at least in part, by differences in solubility of the compounds. The low solubility of hydrocortisone acetate may substantially lessen its alimentary absorption.

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According to a report from the Informacion Medica Española the Spanish Government has allotted money for the provision of homes for doctors; the municipality provides the ground and a large amount of the manpower for the building. The administration of these houses, which include facilities for primary health centres, is under the control of provincial councils. They are placed at the disposal of the medical officer of health of the district, who has two or three rooms for his medical work and five or six for his personal use; he pays a monthly rent not exceeding 2% of the cost of the house, and this is set aside for repairs and upkeep. Each is equipped with examination facilities and everything necessary for emergency operations; all medicaments are supplied by the municipality. So far 200 of these houses have been built, and by the end of this year there should be over 500.

PROGUANIL-RESISTANCE IN MALAYAN STRAINS OF PLASMODIUM VIVAX

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Proguanil (" paludrine ") has been widely used throughout the Federation of Malaya for the prevention of malaria since it first became generally available in 1947. Controlled experiments showed that proguanil in doses of 100–300 mg. once a week was an effective suppressive, and reduced parasite and spleen rates in the semi-immune populations on estates. Overt malaria was usually associated with irregular dosage; transmission, however, was light during the period of these experiments (Institute for Medical Research, 1950).

Proguanil was first used by the Army in Malaya in place of suppressive mepacrine early in 1949, with no apparent change in the malaria sickness rate. The present investigation started as an inquiry into an outbreak of malaria which occurred late in 1950 in a British Army unit engaged in operations against bandits in the Tampin district of the State of Negri Sembilan.

Malaria in the Tampin District

Parts of the Tampin district, and of the surrounding districts, have long been regarded as highly malarious. The Army unit concerned arrived in Malaya in the middle of 1947. The unit headquarters were established in Tampin from then until March, 1950, but detached parties were scattered over a wide area of perhaps 100 miles radius, working in the neighbouring States of Selangor, Pahang, Johore, and Malacca. The incidence of malaria during this period seems to have been low. In March, 1950, the unit was moved to Singapore for about six weeks, returning to Tampin in April, and remaining there until April, 1951, when it left for the Middle East.

The main operational differences between the early period and this later period of twelve months were that the detachments were now all working within a more restricted area, inside a radius of some 30 miles from Tampin, and that the malaria rate for several months was high.

The total strength of the unit was about 600 men, and at any one time perhaps 350 men might be engaged in jungle operations. These figures are merely totals; there was a continual interchange of individuals to and from the unit, and between its various sections. As was the standard Army practice in Malaya, the official suppressive dose was one 100-mg. tablet of proguanil daily.

Four malaria infections occurred between the return from Singapore in mid-April and the end of July, 1950; the sequence of events from then on is shown in Table I.

TABLE I.—*Primary Attacks of Malaria (British Troops Only)*

Parasite Species	1950					1951				Total
	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr. 1–9	
P. falciparum	2	1	3	9	9	4	1	3	3	35
P. vivax ..	4	2	1	7	7	2	3	3	0	29
Total ..	6	3	4	16	16	6	4	6	3	

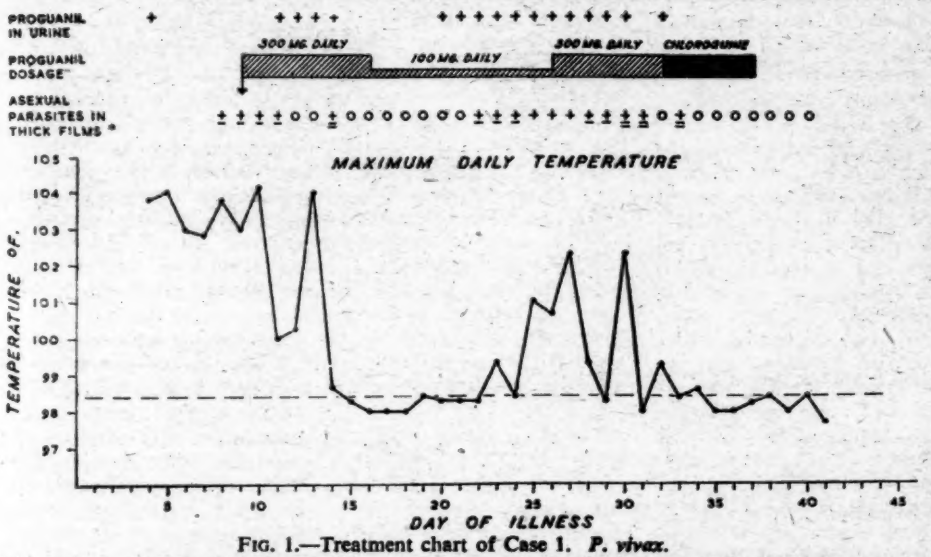

FIG. 1.—Treatment chart of Case 1. *P. vivax.*

**Asexual parasites in thick blood films:* + = Between 1–10 parasites per thick film field. ± = Less than 1 parasite per field, more than 1 in 10 fields. ± = Less than 1 parasite per 10 fields, more than 1 in 100 fields.

The sudden increase in November and December, 1950, and most of the cases occurring thereafter, came from two detachments which had recently started nightly patrols along one particular section of the main railway line.

During the period of just over nine months from July 1, 1950, to April 9, 1951, the Tampin unit, from a strength of about 600 men, supplied 67 admissions for primary attacks of malaria to the Military Hospital at Kuala Lumpur, while other units totalling several thousands supplied only 34 fresh attacks during the same period. The maximum number from any one other unit was eight, and five of these had occurred in one month, October, 1950, from a party operating near the border of the Tampin district. The preponderance of attacks from the Tampin unit was most striking, and caused considerable debate. Either the suppressive discipline was poor or there was something unusual about the malaria parasites of the Tampin district.

The emergence in this area of strains of falciparum malaria resistant to treatment with proguanil had been reported by Edeson and Field (1950). Although the proportion of resistant falciparum infections had increased during the year 1950, haphazard suppression was still regarded as the most likely cause (Institute for Medical Research, 1951). Vivax infections resistant to proguanil treatment had not been encountered; and there had been no indication of any general failure of suppressive proguanil in the civilian population.

Naturally enough, however, suggestions were made that the high malaria rate of the Tampin Army unit might be due, not to irregular suppression, but to infection with parasites which were resistant to prophylactic proguanil. These suggestions were reinforced by the occurrence of 10 primary attacks (5 falciparum, 5 vivax) late in 1950 among men who had arrived in Malaya, after a thorough check of the unit's suppressive discipline had been carried out. None of these 10 men had been in the country for more than three months at the time of his attack; one had been here for only four weeks, and two for only six weeks. So far as could be ascertained, they had taken suppressive proguanil regularly, and nine of them had proguanil present in their urine on the day when first seen by one of us (D. R. R.). Unfortunately this test merely confirmed that proguanil had been taken in the few days immediately preceding; the stories of continuous regular suppressive dosage remained "not proven."

Until January, 1951, there was no proof that any of these infections were proguanil-resistant. Proguanil in the Army was being used solely as a suppressive; acute malaria was treated with mepacrine and/or quinine. The Army medical authorities readily agreed to a proposal that one of us (D. S. M.) should treat vivax infections with proguanil to obtain information about their response to treatment.

The next three patients with acute vivax malaria admitted from the Tampin unit were given a course of 300 mg. of proguanil daily for seven days, after which they immediately reverted to the suppressive dosage of 100 mg. daily, and returned to their unit. Clinical response to treatment was good, but all three were readmitted to hospital with febrile and parasitological relapses 11, 16, and 17 days respectively after resumption of the suppressive dosage. All affirmed that no doses had been missed; none of them had been out on operations since their discharge from hospital, and it seemed that the dose of 100 mg. of proguanil daily had failed to prevent these relapses.

A more strictly supervised investigation was clearly desirable, but unfortunately only three more vivax infections could be so treated before the unit left Malaya; their history is recorded below.

Procedure.—The original diagnosis was made in the Military Hospital laboratory. Once this had been established, duplicate thick blood films were taken daily and stained with Field's rapid stain; one set of these was examined by one of us (T. W.). It will be noted that Cases 1 and 3 were under observation in hospital for four days and seven days respectively before parasites were detected;

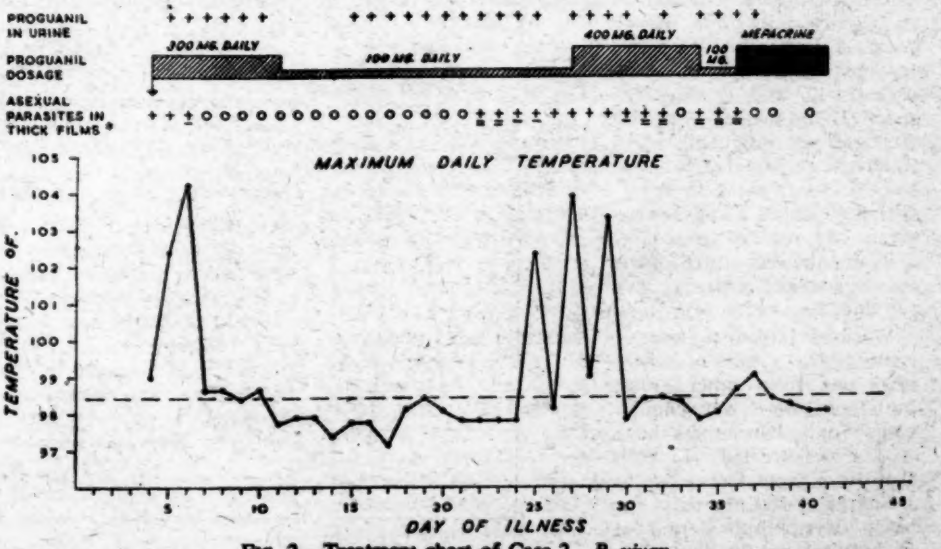

FIG. 2.—Treatment chart of Case 2. *P. vivax.*

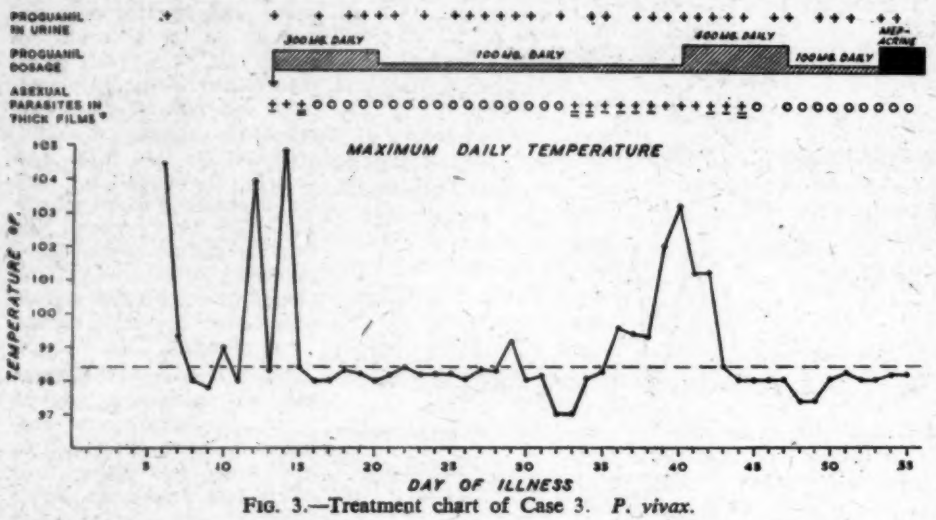

FIG. 3.—Treatment chart of Case 3. *P. vivax.*

during this time no antimalarial drug was given. Proguanil dosage was 300 mg. daily for seven days, after which it was reduced to 100 mg. daily, and the patients remained in hospital under observation. Doses were given by the ward sister, and tests for proguanil in the urine were carried out frequently by the hospital laboratory.

Case Notes

Case 1 (Fig. 1).—Aged 21. In Malaya two and a half years. No previous history of malaria. Ill four days before admission, and blood film taken before being sent to hospital reported negative. Suppressive dosage said to be regular; proguanil present in urine when admitted to hospital.

Case 2 (Fig. 2).—Aged 28. In Malaya two and a half years. History of seven attacks of malaria in past five years, last attack being just over two years earlier. Ill four days before admission. Suppressive dosage said to be regular, but no urine test on day of admission was made.

Case 3 (Fig. 3).—Aged 19. In Malaya three months. No history of malaria. Ill six days before admission, and blood film taken before being sent to hospital reported to contain a few young trophozoites, probably *P. vivax*, but parasites not detected in hospital until seven days later. Suppressive dosage said to have been regular since day after arrival in Malaya; proguanil present in urine on day of admission.

Comment on Cases 1 to 3

All three patients showed a good clinical and parasitological response to the first treatment course of 300 mg. of proguanil daily for seven days. Despite this, parasites reappeared in each of them after 7, 12, and 13 days respectively on the daily dose of 100 mg. of proguanil, duly followed a day or two later by the recurrence of fever. Although Cases 2 and 3 were given 400 mg. of proguanil daily for the second treatment course, parasite clearance was somewhat slower.

We had hoped to treat a comparative series of vivax infections from other areas, but there were not enough cases; only two others have so far been treated. In both there was a good response to a dosage of 300 mg. daily for seven days. Both were kept in hospital for 20 days after resuming the suppressive dose of 100 mg. daily, and so far 120 days have passed with no indication of a relapse.

The unit which took over the Tampin camp and operational areas in April, 1951, was warned of the necessity for rigorous suppressive discipline. No malaria infections occurred during April and May, but the figures since are those given in Table II.

By contrast with the previous year, however, 1951 has seen an increase of malaria among various other Army units in different parts of the country. Staff changes and other reasons unfortunately cut short our therapeutic experiments, and only one vivax malaria patient from the new unit in Tampin could be similarly observed in hospital.

TABLE II

Parasite Species	1951					
	June	July	Aug.	Sept.	Oct. 1–16	Total
P. falciparum ..	3	4	3	12	0	22
P. vivax	1	4	1	13	0	19
Total ..	4	8	4	25	0	41

Case 4 (Fig. 4).—Aged 24. In Malaya 10 months; in Tampin district two and a half months. No history of previous malaria. Ill four days before admission. Proguanil suppression said to have been regular, and proguanil present in urine when patient admitted to hospital.

Comment.—Treatment with 300 mg. of proguanil daily for 10 days gave rather slow parasite clearance in the primary attack. Parasites reappeared after only nine days on the suppressive dose of 100 mg. daily, followed three days later by onset of fever and symptoms; parasites this time persisted throughout a course of 400 mg. daily for 10 days. Reduction of dose to 100 mg. for just one day resulted in an immediate increase in parasites, followed next day by a fresh rise of temperature to 104° F. (40° C.); the attack was then terminated with quinine. This infection was more obviously resistant to proguanil therapy than any of the earlier ones, and apparently had been contracted in the same area.

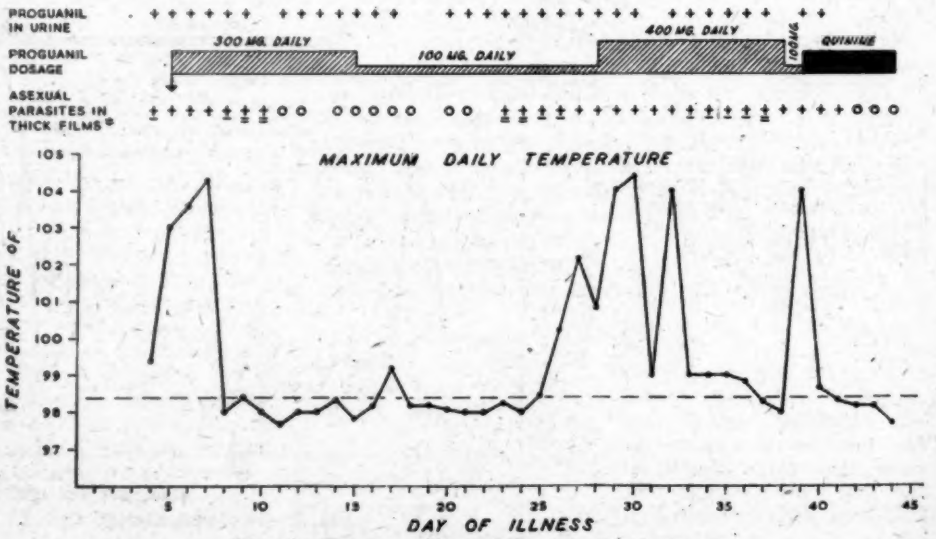

FIG. 4.—Treatment chart of Case 4. *P. vivax.*

Discussion

The occurrence of malaria in persons taking suppressive drugs can be explained in various ways. Fairley *et al.* (1946b), after exhaustive investigation of a large-scale outbreak among troops taking suppressive mepacrine ("atebrin") in the Aitape–Wewak area of New Guinea, decided that both irregular dosage and relative resistance to mepacrine were involved. But resistance to a purely schizonticidal drug like mepacrine presents fewer problems than resistance to proguanil. Fairley *et al.* (1946a) concluded that mepacrine and other schizonticides had no action on the pre-erythrocytic stages of the human malaria parasites; their suppressive effect was due to their action on the asexual parasites reaching the blood at the end of the incubation period. If these blood forms become resistant, then ordinary suppressive doses will fail to prevent an attack.

The prophylactic action of proguanil, on the other hand, was fundamentally different. Proguanil had a direct effect on the pre-erythrocytic forms, and asexual parasites failed to reach the blood. Working with New Guinea strains, we found that in falciparum malaria the pre-erythrocytic forms were destroyed, that in vivax malaria their development was merely inhibited, and that overt malaria might occur after dosage was stopped. Proguanil was also an efficient schizonticide, producing radical cure of falciparum infections; and, although it did not destroy gametocytes, it sterilized them and prevented their development in the mosquito.

Covell *et al.* (1949) confirmed the lethal action of proguanil on the pre-erythrocytic forms of a Lagos strain of *P. falciparum*, and the sterilizing action on gametocytes; clinical cure of acute malaria was obtained, but the infections were not eradicated, and relapses occurred within a few weeks. Ciuca *et al.* (1948), however, found that proguanil did not invariably destroy the pre-erythrocytic forms of a Rumanian strain of *P. falciparum*.

Resistance to proguanil therefore may show itself in various ways. It may be a resistance of the asexual erythrocytic forms or of the pre-erythrocytic forms or of the gametocytes; and certain strains might prove to be resistant throughout the life cycle.

We can do little to resolve the conflict of opinion between those who hold that the excess of malaria in the two Tampin units was due mainly to irregular prophylaxis, and those who favour the idea of infection with strains resistant to prophylactic proguanil. One of us (D. R. R.) was regimental medical officer of the first unit for its last 18 months in Malaya. He considers that suppressive discipline was fair even before September, 1950, and was good from September onwards; the ten infections mentioned above as occurring in new arrivals after October, 1950, developed, he thinks, despite a regular prophylactic dosage from the time of reaching the country. To this opinion may be added a number of similar complaints from Africa (Davey and Smith, 1949; Bruce-Chwatt and Bruce-Chwatt, 1950; MacLeod, 1951), but proof of regular dosage was unobtainable in many of the examples given. We cannot be certain how many of the Tampin infections were due to irregular prophylactic dosage, but we suggest that some at least may have occurred in men who took their doses regularly.

Reverting to our therapeutic findings, it seems that probably in the first three patients, and certainly in the four observed in hospital, we were dealing with erythrocytic forms of *P. vivax* which were only temporarily suppressed by daily doses of 300 mg. of proguanil, and which could multiply sufficiently to produce clinical and parasitological relapses while 100 mg. daily was still being taken. Malayan strains of *P. vivax* had hitherto proved very sensitive to treatment with proguanil (Institute of Medical Research, 1950),* and the two vivax infections from other areas had not relapsed over a much longer period. How might this degree of resistance have been produced, and what were the implications?

Experimentally, the erythrocytic forms of both *P. falciparum* and *P. vivax* have been rendered resistant to proguanil treatment by exposing them repeatedly to inadequate doses (Seaton and Adams, 1949; Seaton and Lourie, 1949; Cooper *et al.*, 1950a); but prolonged dosage during the pre-erythrocytic stage of *P. vivax* did not induce resistance in the erythrocytic forms which appeared after dosage was stopped (Cooper *et al.*, 1950b). We think it unlikely that each of our patients was originally infected with a sensitive strain which he then transmuted into resistant forms by widely spaced doses during sporadic bursts of parasitaemia, but this possibility cannot be dismissed entirely; three of the four patients had been in the country for ten months or more, though only one was known to have had malaria before. Such a method of producing resistant erythrocytic forms would seem to be ruled out for Case 3, who had been here for only three months. This man did not arrive in Malaya until December, 1950, by which time a great deal of attention had been paid to the suppressive discipline of his unit. He had no history of previous fever, and the parasite level at which he originally developed symptoms was low, indicating that this was probably a primary attack. We suggest that the balance of evidence is in favour of another hypothesis—namely, that these men had been infected by a strain of vivax malaria whose erythrocytic forms had already developed a partial resistance to proguanil.

Seaton and Adams (1949) and Seaton and Lourie (1949) have proved that when the erythrocytic forms of *P. falciparum* and *P. vivax* have become resistant to proguanil the erythrocytic parasites which appear in fresh victims, after mosquito passage of the infection, are also resistant. It is thus possible that under suitable local conditions mosquitoes may be transmitting strains of malaria whose erythrocytic forms are relatively resistant, as in these patients of ours. Confronted with this possibility, the medical officer in the Tropics wants to know, among other things, whether proguanil-resistance of the erythrocytic forms automatically implies a change in the response of the pre-erythrocytic forms to proguanil prophylaxis. If the erythrocytic forms are resistant, can the pre-erythrocytic forms of that particular strain complete their development despite a regular prophylactic dosage from the time of infection, and will proguanil thus be as powerless to prevent clinical attacks as it is to cure them when they occur?

Oddly enough, the experimental workers have not yet provided an answer to this most important question. The experiments on proguanil prophylaxis with human malaria parasites all seem to have been made on strains which responded well to proguanil treatment of acute attacks; this was so even with the Lagos strain of *P. falciparum* investigated by Covell *et al.* (1949). The only report of a prophylatic experiment with a resistant strain which we have seen is one by Hawking and Thurston (1951) on *P. cynomolgi* in monkeys. Proguanil given shortly before sporozoite inoculation, and daily for seven days afterwards, prolonged the incubation period by only one day in the treated monkey compared with an untreated control. There is unfortunately no indication of how the original proguanil-sensitive strain behaved when treated in the same way.

In Malaya to date, and probably elsewhere, strains of human malaria refractory to proguanil therapy occur only sporadically, yet their appearance has prompted the recommendation that proguanil should not be used by itself for the treatment of acute falciparum malaria. But the drug is being distributed as a suppressive on a very large scale, often without supervision, and there are indications that such resistant strains are becoming more common; the danger, therefore, is that they will become widespread. Before that occurs, the field worker needs to know whether proguanil can still be relied upon as a prophylactic against these strains, or whether he must seek elsewhere for protection. Clearly

*Dr. J. F. B. Edeson (personal communication) reports one resistant vivax infection in April, 1951, in Tampin Hospital, with asexual parasites still present on the seventh day of treatment with 300 mg. of proguanil daily.

we need a controlled experiment in proguanil prophylaxis, comparing proguanil-sensitive and proguanil-resistant strains of human malaria parasites, to decide whether there is in fact any significant difference in their response to regular prophylactic doses.

Summary

Fresh infections of falciparum and vivax malaria occurred late in the year 1950 among British troops in the Tampin district of Negri Sembilan, Federation of Malaya, shortly after they had started night patrols in one particular locality.

A similar incidence of malaria occurred in 1951 among troops from a different unit operating in the same areas.

The troops were on an official suppressive dosage of 100 mg. of proguanil daily, and suppressive discipline was thought to be good.

Treatment of some of the vivax infections revealed that their erythrocytic parasites were only temporarily suppressed by doses of 300 mg. of proguanil daily for 7 to 10 days. Parasitological and clinical relapses occurred 7 to 17 days after reverting to the normal suppressive dose of 100 mg. daily. One of these patients had been only three months in Malaya, and had been on regular suppressive proguanil from the day after arrival.

Possible explanations for these findings are discussed. Irregular dosage cannot be excluded as a possible cause of the incidence of malaria in the Tampin units, but it is thought that some infections may have developed in men who took their suppressive doses regularly. It is suggested that the proguanil-treated vivax patients may have been infected with a strain whose erythrocytic parasites were already partially resistant. If this may happen, as seems possible, then controlled experiments are needed to determine whether resistance of erythrocytic forms also implies that pre-erythrocytic forms may complete their development, and produce clinical attacks of malaria, despite regular prophylactic dosage from the time of infection.

Our thanks are due to Colonel P. F. Palmer, late R.A.M.C., A.D.M.S. Malaya, for permission to treat these patients; to Colonel D. W. Hughes, late R.A.M.C., Consultant Physician, FARELF, for criticism and advice, and to Brigadier R. Murphy, late R.A.M.C., D.M.S., FARELF, for permission to publish.

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The production of films covering the field of medicine and surgery is being encouraged in Spain by a newly created Association of Medical Cinematography. Exchange of similar films with foreign countries is planned. The general secretarial work is being undertaken by Dr. don Juan Fernán Pérez, calle de Fuencarral, No. 113, Madrid. He is director of *Vida Sana* and medical editor of the daily paper *Madrid*.

CHEMOTHERAPY AND CHEMOPROPHYLAXIS OF MALARIA

CLINICAL TRIALS IN 500 CASES AND MASS PROPHYLAXIS IN A HYPERENDEMIC AREA

BY

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During the past three or four years a number of new drugs have been tested at the Calcutta School of Tropical Medicine for their therapeutic and suppressive values in malaria. The patients admitted to the attached hospital were utilized for the purpose, but the main work on the suppressive therapy was carried out in a rural area about 40 miles from Calcutta. A summary of the work is given in Tables II and III.

I. CHEMOTHERAPY

Only those patients who had fever with parasites in the blood and had no antimalarial drug outside were selected for the trials. The blood was examined twice daily (thick film method, using Field (1941) or J. S. B.* stain) until it became negative for asexual parasites, and thereafter once daily throughout the period of hospital observation. Of the 500 cases examined 51% had *P. vivax* and 42% *P. falciparum* infection; the rest had mixed (4.4%) or *P. malariae* (2.6%) infection. The following drugs were tried:

TABLE I.—*Schedules of Treatment*

No.	Compound Used	Route of Administration	No. of Cases
1	Proguanil (paludrine)	(A) Oral	209
		(B) Intravenous*	12
		(C) Intramuscular	12
2	Proguanil + pamaquin	Oral	30
3	Quino-pamaquin	,,	13
4	M.5943	,,	18
5	Chloroquine	,,	75
6	Chloroquine + proguanil	,,	13
7	Camoquin	,,	80
8	Camoquin + proguanil	,,	8
9–13	Neochin and other 4 indigenous drugs	,,	30
			500

* One patient also had oral and intramuscular proguanil in addition to intravenous therapy.

1. Proguanil

Effect on Temperature and Parasite.—The usual route of administration was by mouth, and in only a small number of cases was the parenteral method used. Orally, various dosage schedules were tried either in a single dose of 0.1 to 0.8 g. or in divided doses of 0.3 to 0.8 g. given daily over 4 to 10 days. With any of these regimes an acute attack was terminated on the third day in most cases. A daily dose of 0.3 to 0.6 g., however, seemed to produce the best results, and we think that a course of 1.8 g. given over five

*Jaswant Singh and Bhattacharji (1944).

TABLE II.—*Chemotherapy of Malaria*

Drug	Group	Dosage	No. of Cases					Total	Time for Fever to Subside		Time for Asexual Parasites to Disappear		Relapse Rate	Observation Period
			F.	V.	M.	F.+V.	F.+M.		1–3 Days	4 Days or More	1–3 Days	4 Days or More		
Proguanil hydrochloride (87% base)	1	Single dose: 0·1 g. (salt)	7	2	1	1	0	11	8 (72%)	3 (28%)	9 (81%)	2 (19%)	6 (4 F., 1 M., 1 F.+V.) out of 8 (5 F., 1 V., 1 M., 1 F.+V.) = 75%	14–55 days in hospital
	2	Single dose: 0·3 g. (salt)	26	16	0	0	0	42	37 (88%)	5 (12%)	37 (88%)	5 (12%)	6 (5 F., 1 V.) out of 22 (13 F., 9 V.) = 27%	14–30 days in hospital
	3	Single dose: 0·5 g. (salt)	12	12	0	1	0	25	21 (84%)	4 (16%)	21 (84%)	4 (16%)	9 (5 F., 4 V.) out of 22 (11 F., 10 V., 1 F.+V.) = 41%	14–120 days (7 cases relapsed within a month)
	4 5	Single dose: 0·6 g. (salt), 4 cases 0·8 g. (salt), 8 cases	6	6	0	0	0	12	8 (67%)	4 (33%)	8 (67%)	4 (33%)	4 out of 12 = 33%	Average: 3 weeks in hospital
	6	Divided dose: 0·1 g. t.d.s. 4 days = 1·2 g.	20	21	1	2	0	44	35 (80%)	9 (20%)	41 (93%)	3 (7%)	5 out of 12 = 42%	4–6 months
	7	Divided dose: 0·6 g. (in 2 doses) on 1st day and 0·3 g. daily for next 3 or 4 days = 1·5 to 1·8 g.	4	14	0	0	0	18	16 (89%)	2 (11%)	18 (100%)	Nil	No relapse	Average: 3 weeks in hospital—9 followed up for 2 months
	8	Divided dose: 0·2 g. (salt) 6-hourly for 4 days = 3·2 g.	3	7	1	1	0	12	8 (67%)	4 (33%)	8 (67%)	4 (33%)	2 vivax relapse	Average: 3 weeks in hospital
	9	Divided dose: 0·1 g. (salt) t.d.s. for 10 days = 3 g.	12	13	0	0	0	25	21 (84%)	4 (16%)	23 (92%)	2 (8%)	2 falciparum relapse	Average: 3 weeks in hospital
	10	Divided dose: 0·3 g. (salt) b.d. for 10 days = 6 g.	14	6	0	0	0	20	16 (80%)	4 (20%)	18 (90%)	2 (10%)	1 relapse	Average: 3 weeks in hospital
Proguanil lactate (74% base)	11	Single dose: 0·1–0·3 g. (lactate) intramuscularly	3	6	2	0	1	12	8 (67%)	4 (33%)	11 (92%)	1 (8%)	4 (3 F., 1 V.) out of 12 (3 in hospital and 1 after discharge) = 33%	8–42 days in hospital
Proguanil acetate (79% base)	12	Divided dose: 0·2–0·6 g. (acetate) intravenously	9	2	0	1	0	12	10 (83%)	2 (17%)	10 (83%)	2 (17%)	1 (F.+V.) out of 3 (2 F., 1 F.+V.)	6–8 months
Proguanil hydrochloride and pamaquin naphthoate (45% base)	13	Proguanil 0·3 g. (salt) and pamaquin 0·01 g. (base) b.d. for 10 days	0	30	0	0	0	30	27 (90%)	3 (10%)	29 (97%)	1 (3%)	4* out of 14 = 29%	Average 3 months
Quinine sulphate (82% base) and pamaquin naphthoate	14	Quinine sulphate 0·33 g. (5 gr.) and pamaquin 0·01 g. (base) t.d.s. for 10 days	0	13	0	0	0	13	13 (100%)	Nil	13 (100%)	Nil	1 out of 13 = 8%	Average 3 months
M.5943 (88% base) ..	15	Divided dose: 0·02 g. t.d.s. for 10 days	0	17	1	0	0	18	17 (94%)	1 (6%)	16 (89%)	2 (11%)	3 out of 18 = 17%	Average 3 months
Chloroquine diphosphate (62% base)	16 17	Divided dose: 1·25 g. (base), 42 cases Single dose: 1·5 g. (base), 8 cases	18	27	1	4	0	50	50 (100%)	Nil	49 (98%)	1 (2%)	4 (2 F., 2 V.) out of 20 = 20%	1–7 months
	18	Single dose: 0·5 g. (base)	10	15	0	0	0	25	25 (100%)	Nil	25 (100%)	Nil	2 (1 F., 1 V.) out of 12 = 17%	1–3 months
Chloroquine diphosphate and proguanil hydrochloride	19	Chloroquine: single dose of 0·5 g. (base) on 1st day and proguanil hydrochloride 0·3 g. b.d. for next 6 days	11	0	0	2	0	13	13 (100%)	Nil	13 (100%)	Nil	No relapse in hospital	15–53 days in hospital
Camoquin dihydrochloride dihydrate (77% base)	20	Single dose: 0·5 g. (base)	20	25	5	2	1	53	53 (100%)	Nil	53 (100%)	Nil	8 (3 F., 5 V.) out of 33 = 24%	1–8 months
	21	Divided dose: 0·1 g. (base) b.d. for 3 days = 0·6 g.	12	11	0	4	0	27	26 (96%)	1 (4%)	27 (100%)	Nil	6 (1 F., 5 V.) out of 8 = 75%	1–8 months
Camoquin dihydrochloride dihydrate and proguanil hydrochloride	22	Camoquin: single dose of 0·5 g. (base) on 1st day and paludrine hydrochloride 0·3 g. b.d. for next 6 days	6	2	0	0	0	8	8 (100%)	Nil	8 (100%)	Nil	One falciparum relapse after three weeks	21–50 days

* One other case had subclinical parasitic relapse detected by subinoculation.

TABLE III.—*Chemoprophylaxis of Malaria*

Drug	Group	Parasite Rate										1949–50 Malaria Incidence Rate bet. Sept. 30 and Dec. 30, 1949	Spleen Rate			
		1948–9				1949–50							1948–9		1949–50	
		May, 1948	Sept., 1948	Nov., 1948	Feb., 1949	May, 1949	July, 1949	Sept., 1949	Nov., 1949	Feb., 1950	May, 1950		May, 1948	Feb., 1949	Oct., 1949	Feb., 1950
Proguanil hydrochloride, 0·1 g. twice weekly	I	11·20 (235)	3·15 (222)	4·48 (223)	1·36 (221)	4·10 (167)	4·58 (153)	7·73 (194)	2·86 (175)	2·15 (186)	6·16 (211)	21·54*	55·4	24·4	33·0	26·8
Proguanil hydrochloride, 0·3 g. once weekly	II	9·42 (276)	9·13 (219)	5·73 (227)	3·09 (259)	9·56 (241)	12·50 (216)	8·00 (200)	7·65 (196)	5·31 (207)	11·6 (190)	12·28	72·8	35·6	33·5	26·0
Camoquin, 0·2 g. base once weekly	III	10·57 (246)	9·02 (212)	1·89 (212)	0·63 (159)	5·95 (84)	16·13 (155)	6·17 (162)	0·67 (149)	0·66 (151)	3·2 (217)	3·12	64·2	16·4	26·3	12·4
Chloroquine, 0·25 g. base once weekly	IV	7·90 (227)	5·90 (101)	2·60 (193)	1·60 (261)	1·87 (190)	7·09 (141)	0·00 (149)	0·00 (146)	2·16 (139)	2·0 (200)	3·27	57·7	18·2	25·7	8·8
Quinine sulphate, 0·33 g. (5 gr.) twice weekly	V	—	—	—	—	—	5·19 (289)	6·05 (21)	4·04 (198)	4·23 (189)	—	26·15*	—	—	53·4	43·1
Control (quinine for acute attacks only)	VI	11·32 (265)	15·03 (173)	36·87 (179)	14·57 (199)	17·4 (224)	6·82	9·32	15·57	13·33	22·2 (216)	62·98	61·2	50·6	54·2	55·4

The drugs were administered for 26 weeks from July to December in the first five groups and the sixth group served as a control. The observations were carried out through two transmission seasons and are referred to here as 1948–9 and 1949–50 experiments. The parasite rate, malaria incidence rate, and spleen rate are all expressed in percentages. The figures in parentheses indicate the number of cases examined at different stages of the experiment.

* The higher incidence rate in these two groups may be partly due to the mode of collection of data; they were paid two visits a week as compared with one visit a week in the other groups.

days—that is, 0.6 g. in two doses on the first day and 0.3 g. on the next four days—is sufficient to terminate a malarial attack in an average case unless one encounters a refractory strain. A higher dose has not been of any advantage either in controlling the acute attack or in preventing relapses. For reducing the relapse rate of vivax or malariae infection, however, it should be combined with pamaquin, or be followed by weekly proguanil (0.3 g.) as long as possible. We found the drug about equally active, though relatively slow, against falciparum and vivax types of parasites. It has no influence on the appearance of crescents in the peripheral blood; these tend to persist for a long time, the maximum period noted being two months.

Absorption and Excretion.—For determination of proguanil concentration in the blood the hydrolytic method of Spinks and Tottey (1946) was used. The level of proguanil varied with different individuals, but in general it was proportionate to the dose of the drug. There was a rapid rise in the concentration of the blood after four hours; it was reduced nearly to half on the second day, and usually by the fourth day it was down to negligible figures. About the same kind of result was obtained after intramuscular administration. It was also observed that the drug disappeared from the urine generally in four to five days, most of it being excreted during the first 48 hours. The total excretion varied from 37 to 54% of the drug administered.

Toxicity.—No toxic reactions were noticed except in patients who were having large amounts of the drug. With 0.8 g. given in a single dose or in daily divided doses, gastro-intestinal irritation with nausea, vomiting, diarrhoea, and griping was the commonest untoward reaction, but renal irritation was noticed in two patients (0.2 g. six-hourly for four days), one of them having frank haematuria with pain in the loins. The withdrawal of the drug gave prompt relief, but in some patients the treatment was continued without any ill effect. In a few cases (0.3 g. twice daily for 10 days) gastric irritation was noticed towards the end of the course, and on this account treatment was discontinued about the seventh day.

Relapses.—The working of the relapse rate is rather difficult in India, where people are constantly exposed to the risk of infection. Many of the relapse cases, however, developed the attack in the hospital or under conditions where the chance of reinfection was unlikely. Owing to the unavoidable uncertainty, we have lately laid more stress on the early relapses and kept most of our patients in hospital for at least a month under observation. Judging in this way, we found that early relapses were more infrequent with divided proguanil dosage given for 4 to 10 days than with single doses. But even with proper dosage the cases that have been followed up for three to six months have shown a relapse rate of the order of 40%. The actual relapse rates for different observation periods are shown in Table I, from which it will be evident that the single-dose treatment always leads to a high early relapse rate, indicating the inadequacy of that method of treatment. We are therefore of the opinion that the single-dose treatment with proguanil should be abandoned.

Resistance to Proguanil.—We have encountered some cases of falciparum infection that proved refractory to proguanil. In one case the drug had no effect on the fever and parasites, and resistance of the particular strain was also shown in a second volunteer who was inoculated with the blood of the first patient and developed malaria which did not respond to intensive proguanil therapy. In another case there were repeated early relapses, indicating that the parasite was resistant and could not be completely eradicated with proguanil. Besides these we had two fatal cases of malaria: (1) a girl of 9 admitted in a restless and delirious state; and (2) a man of 75 with 35.6% of red cells infected with falciparum rings (some red cells containing two, three, or four rings) and a few schizonts and crescents. The girl had two intravenous injections, 0.1 g. each, before she died 16 hours after admission, while the old man had 1.4 g. of proguanil (parenterally and orally) in the course of the 34 hours he was alive in the hospital. A necropsy in this case showed intense proliferation of the parasites in the internal organs, though their number in the peripheral blood had been reduced. The first patient was severely ill and the second had a very heavy infection, so it is difficult to say what would have happened if more potent antimalarial drugs had been used.

Parenteral Proguanil.—This was given intravenously or intramuscularly, 12 cases by each method, and the results are shown in Table IV.

TABLE IV.—*Parenteral Proguanil: Effect on Temperature and Asexual Parasites*

Route	Total Cases	Infection					Last Day of Fever						Last Day of Parasites					
		F.	V.	M.	V.+F.	F.+M.	1	2	3	4	5	Dth.	1	2	3	4	5	Dth.
I.V.	12	9	2	0	1	0	1	4	5	0	0	2	0	7	3	0	0	2
I.M.	12	3	6	2	0	1	2*	1	5	3	1	0	1	5	5	0	1	0

* One of these patients, a case of quartan malaria, received the drug in the apyrexial period and the next paroxysm was suppressed.

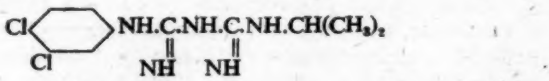
Intravenous Proguanil.—Proguanil acetate or lactate was tried as an experimental measure in a series of 12 cases of malaria, all except two of which had falciparum infection. Two of the patients in this series, already mentioned above, died. The injections (up to 400 mg. at a time) were well tolerated by some, but two patients had phlebitis of the injected vein (which subsided in a few days), one had a severe reaction (collapse) after the injection, and another developed

symptoms suggestive of encephalitis, though it could not be definitely said whether it was the effect of the drug or of the disease. The symptoms eventually cleared up within about two months.

Intramuscular Proguanil.—Proguanil lactate (0.1 g. in 2-ml. ampoules) was tried in a single dose varying from 0.1 to 0.3 g. The results were somewhat like those obtained with oral proguanil. All the three *P. malariae* cases in this series responded to a single injection of 0.1 g., and no recrudescence occurred within four to six weeks while they were in the hospital. One of them had regular paroxysms for one year interrupted only for a fortnight by quinine, with a splenic enlargement to 9 in. (23 cm.) below the costal margin. The injection controlled the paroxysm and the patient was discharged after a month with a spleen reduced to only 3 in. (7.5 cm.) below the costal margin. The intramuscular injections were painful (more than with quinine), but the pain, local induration, and tenderness did not usually persist beyond the third day and left no sequelae, except in one case in which there was a local blister formation which gradually dried up.

2. Quino-Pamaquin, Proguanil-Pamaquin, and M.5943

These drugs were tried in 60 vivax and one malariae infection, mainly with the object of ascertaining the relapse rates. Quino-pamaquin is already a well-known remedy for the radical cure of recurring vivax malaria, and was adopted as a standard for comparison. M.5943 is a new synthetic compound. During their study of the antimalarial properties of diguanide substances related to proguanil, Curd, Davey, Hendry, and Rose (1950), of the Research Laboratories of Imperial Chemical Industries, Manchester, obtained the impression that weighting the benzene ring augmented activity. They therefore prepared a number of compounds in which *di*-substitution was made in the benzene ring. Dihalogen substitution in positions 3 and 4 proved particularly favourable for antimalarial activity. A representative compound, N_1-3:4-dichlorphenyl-N_5-isopropyl diguanide (given the laboratory number M.5943), was chosen for trial in human malaria. M.5943 differs from proguanil only in having an extra Cl group in position 3 of the benzene ring. Its constitution is:



M.5943 was tested against *P. gallinaceum* and *P. relictum* (Algerian strain) by Davey (1946a, 1946b) and was found to be much more active than proguanil against both the blood forms and the exoerythrocytic forms of these parasites. We are reporting here the results of treatment with M.5943 in vivax malaria as compared with combined courses of quino-pamaquin and proguanil-pamaquin.

TABLE V.—*M.5943, Quino-Pamaquin and Proguanil-Pamaquin in Vivax Malaria*

	Quinine 5 gr. (0·32 g.) + Pamaquin 10 mg. (Base) t.d.s. for 10 Days	Proguanil hydrochloride 0·3 g. + Pamaquin 10 mg. (Base) b.d. for 10 Days	M.5943 20 mg t.d.s. for 10 Days
No. of cases	13 (V.)	14 (V.)	18 (17 V.+1 M.)
Average duration of fever (days)	1·1	1·8	1·8
Average duration of parasite in blood (days)	1·8	2·0	2·2
Gametocytes: Cleared in 3 days ..	100%	86%	67%
Persisted for 4 or 5 days	Nil	14%	33%
Relapse rate (average period of observation, 3 months)	8%	29%	17%

Table V shows that the best immediate result was obtained with quino-pamaquin, both proguanil-pamaquin and M.5943 being slower and equal in action. M.5943 appears to be rather slowly active against *P. malariae*, the temperature and parasites in the single case having persisted for five days. All the three drugs cleared the peripheral blood of the vivax or malariae gametocytes, and this property was most marked with quino-pamaquin, which was also better than the other two in respect of both immediate action and relapses. The difference in the gametocidal property of the first two combinations, however, may be due to the higher dose of pamaquin—namely, 30 mg. daily used in the first as compared with 20 mg. in the second.

Relapses.—The relapse rate in a follow-up for an average period of three months in the 45 cases observed in 1949 worked out at 17% (3 cases) for M.5943, 29% (4 cases) for proguanil-pamaquin, and 8% (1 case) for quino-pamaquin. Another subclinical relapse in the second series was detected accidentally by the development of febrile malaria in the recipient of a blood transfusion from the said case. If this is included the relapse rate in the proguanil-pamaquin series rises to 36%. If all the 30 cases (including 16 cases treated in the previous year) of the proguanil-pamaquin series are taken together, however, the relapse rate works out at 20%. There is no significant difference in the interval of freedom of attack prior to relapse in the three groups.

Toxicity.—Two cases in the proguanil-pamaquin series showed rather severe toxic reactions (nausea, vomiting, palpitation, and depression) and could not take the full course. No significant side-effect was noticed with quino-pamaquin. In the M.5943 group seven patients had toxic reactions—namely, nausea, vomiting, and/or abdominal pain. One patient complained of bleeding from the gums and another of dysuria during the course, but it cannot be definitely stated that they were entirely due to the drug. The treatment had to be interrupted for a day or two in a few cases for these reactions, and was then resumed in the same or slightly reduced dosage.

3. Chloroquine

Effect on Temperature and Parasites.—Chloroquine was tried in either single or divided doses in a series of 75 patients. The clinical response was very prompt with each regime, and fever and parasitaemia were controlled by the third day in all except one case. With 1.5 g. (base) in a single dose or 1.25 g. in divided doses, 96% became afebrile and 80% parasite-free in two days in a series of 50 patients: these figures were 84% and 100%, respectively, in another series of 25 patients treated with a single dose of 0.5 g. We have not had such an excellent result with any other antimalarial drug. We found it somewhat more active against vivax than against falciparum infection.

TABLE VI.—*Action of Chloroquine on P. falciparum and P. vivax*

Infection	No. of Cases	Last Day of Fever				Last Day of Asexual Parasite			
		1	2	3	4	1	2	3	4
P. falciparum	29	17 59%	7 24%	5 17%	0	12 41%	11 38%	5 17%	1 3%
P. vivax ..	41	23 56%	17 41%	1 3%	0	20 49%	17 41%	4 10%	0

It will be seen from Table VI that, while fever had subsided in 83% and asexual parasites disappeared in 79% in two days in falciparum infection, the corresponding figures from vivax infection are 97% and 90%. The drug has little or no action on gametocytes, the crescents having been found up to 22 days after treatment.

Toxicity.—Some untoward effect of the drug was observed in 5 of the 50 cases (10%) treated with 1.25 or 1.5 g. of the basic drug. Complaint was made of one or more of the following symptoms, which usually disappeared in two days; insomnia, gastro-intestinal irritation, pruritus (especially in the hands and feet), and pain in the lower abdomen, genitalia, and thighs (1 case). Another patient, not included in this series, had epileptiform fits after taking the drug.

Relapses.—Four patients relapsed out of 20 who had 1.5 g. (single dose) or 1.25 g. (divided doses) and who could be followed up for one to seven months: two with falciparum infection after 30 and 45 days, and two with vivax infection after 45 and 210 days. Two (one falciparum and one vivax) out of 12 patients given a single dose of 0.5 g., and who were followed up to three months, relapsed after 53 and 49 days respectively. None of the patients had an early recrudescence in the hospital with either regime, unlike the cases under proguanil. In fact, relapses were much less common with chloroquine.

4. Camoquin

Camoquin is almost as potent a drug as chloroquine. A single dose of 0.5 g. of the basic drug terminated fever and cleared the parasites in two days in 86% and 83% of the 52 cases respectively. This single-dose treatment was better than the divided dose of 0.1 g. twice daily for three days, which in a series of 27 cases gave the corresponding figures as 74% and 81%. It is almost equally effective against vivax, falciparum, and malariae infections. It has no action on crescents, which were seen in the blood up to 26 days, but the vivax and malariae gametocytes disappeared in one to five days.

Toxicity.—The drug was well tolerated and no untoward symptoms were noticed even in cases with severe anaemia.

Relapses.—Here also the single-dose treatment gave better results. Out of 33 patients who had a single dose of 0.5 g., 8 (3 falciparum and 5 vivax) relapsed, while 6 out of 8 patients who had 0.6 g. over three days relapsed, in each case after an interval varying from 2 to 30 weeks. All of them were under observation for one to eight months. The high relapse rate and lower potency of the divided dose would appear to be due to inadequacy of dosage, and will, we think, be improved by giving an initial loading dose.

5. Chloroquine or Camoquin in Combination with Proguanil

Since infections with *P. falciparum* may prove refractory to proguanil alone, we used that drug in combination with chloroquine or camoquin in two series of cases, and 21 patients have so far been treated in this manner. The effect on temperature and parasitaemia is shown in Table VII.

TABLE VII.—*Effect of Combined Chloroquine-Proguanil and Camoquin-Proguanil on Temperature and Parasitaemia*

Drug and Dose	Infection	No. of Cases	Last Day of Fever				Last Day of Parasitaemia (Asexual)			
			1	2	3	4	1	2	3	4
Chloroquine, 0·5 g. base on 1st day, and proguanil hydrochloride, 0·3 g. b.d., for next six days	F. F.V.	11 2	7 1	3 1	1 0	0 0	1 1	8 1	2 0	0 0
Total ..		13	8	4	1	0	2	9	2	0
			92·5%				84·6%			
Camoquin, 0·5 g. base on 1st day, and proguanil hydrochloride, 0·3 g. b.d., next 6 days	F. V.	6 2	1 0	4 1	1 1	0 0	3 0	1 1	2 1	0 0
Total ..		8	1	5	2	0	3	2	3	0
			75%				62·5%			

It will be seen that this method of treatment rapidly terminated the malarial attack. The results are comparable to those obtained with single doses of camoquin or chloroquine alone. But proguanil alone would have been slower in action, and its reinforcement on the first day by a single dose of chloroquine or camoquin seems to have had a greater effect than quinine or mepacrine in similar conditions.

There were no toxic reactions, and only one case in the camoquin-proguanil series out of the 21 cases treated relapsed after three weeks in a follow-up period of 15–53 days in the hospital.

6. Indigenous Drugs

Neochin, which is dicinchonine carbonate, had a poor antimalarial property, and the other drugs were useless.

Conclusion

Chloroquine and camoquin are the two outstanding drugs in the treatment of malaria. Even with a single dose they can effect a clinical cure in most cases in two days, with disappearance of asexual parasites. Proguanil is also effective, but has a slower action, and resistant falciparum cases are occasionally encountered. The optimum effective dose in our cases has been chloroquine (base), 0.5 g. immediately, 0.25 g. after six hours, and 0.25 g. on the second and third days; camoquin (base), 0.5 g. (or three 0.2 g. tablets) in a single dose; and proguanil hydrochloride, 0.3 g. twice daily on the first day and 0.3 g. once daily for the next four days. The toxic effects of proguanil are usually insignificant, but may result from large doses. So far no toxicity has been observed with camoquin, while about 10% of chloroquine cases had temporary untoward reactions in the doses used. These drugs, however, do not solve the problem of vivax relapses, which can at present be reduced by giving quino-pamaquin, which is more effective than proguanil-pamaquin, or suppressed by weekly doses of one of the above drugs. M.5943 has no advantage over other antimalarials.

II. CHEMOPROPHYLAXIS

Prophylactic trials were carried out in two successive years, 1948 and 1949, in a hyperendemic rural area, about 40 miles (64 km.) from Calcutta, comprising 10 villages with a population of 1,458. The people were mostly land workers in a poor nutritional condition. The overall spleen and parasite rates were 62.8% and 10.7% respectively, while the corresponding rates for children under 10, who formed nearly one-third of the population, were 58.5% and 17.4%. The work was started with five groups of the population each consisting of about 250 people—four having proguanil, camoquin, or chloroquine (groups I to IV, see Table III), and one serving as control (group VI). In 1949, in addition to these five groups, an extra group (V) was given bi-weekly quinine prophylaxis, and a subgroup (IIIA) of about 50 people had camoquin prophylaxis in a reduced dosage. The details are shown in Table VIII.

The drugs were administered throughout the transmission period from July to December. Blood was examined every two or three months, but the spleen was examined only at the beginning and end of the prophylactic period. The incidence of malaria in those taking the drugs was judged by examining the blood of those who had fever. To the control group no drug was administered except a few doses of quinine to control the acute attacks. No anti-mosquito measures were adopted in the whole area.

Parasite Rate

Compared with the control group malaria was definitely under check, the parasite rate remaining more or less low according to the drug used. In May, 1948, prior to the first experiment, the average infection rate in these villages was 10 per 100. In November, 1948, this rose to 37 in the control group (October and November are here the usual peak

TABLE VIII.—*Schedule of Chemoprophylaxis*

Group	No. of Subjects	Drug Used and Frequency of Administration	Dose			Year of Trial	Initial Spleen Rate %	Initial Parasite Rate %
			>10 yrs.	4–10 yrs.	<4 yrs.			
I	235	Proguanil hydrochloride twice weekly	0·1 g.	0·05 g.	0·03 g.	1948–9	55·4	12
II	276	Proguanil hydrochloride once weekly	0·3 ,,	0·2 ,,	0·1 ,,	1948–9	72·8	9·42
III	246	Camoquin* once weekly	0·2 ,,	0·1 ,,	0·05 ,,	1948–9	64·2	10·57
IV	227	Chloroquine* once weekly	0·25 ,,	0·125 ,,	0·062 ,,	1948–9	57·7	7·9
V	289	Quinine sulphate twice weekly	5 gr.	2½ gr.	2½ gr.	1949	53·4	5·19
VI	265	No drug—prophylaxis (control)				1948–9	61·2	11·32

* Dosage of camoquin and chloroquine is expressed in base.

period of malaria), while the parasite rates in the treated groups varied from 2 to 6, the best results being obtained with camoquin and chloroquine. As regards proguanil, there was some superiority of the bi-weekly group (I) to the weekly regime (II). In 1949 the results were still more remarkable. The control group showed a parasite rate of 15.57 in the month of November—a much lower peak than in the previous year owing to lessened severity of malaria that year or to unexplained factors, whereas the corresponding figures for chloroquine (IV), camoquin (III), and bi-weekly proguanil (I) were 0.00, 0.67, and 2.86 respectively. With the last regime, however, there was a rise in the parasite rate in September, 1949, by almost 50% above the rate in July, 1949, the cause for which is not understood.

In striking contrast to the results in the three groups mentioned above, the weekly proguanil regime (II) was less effective, with a parasite rate of 7.65 against the previous year's figure of 5.73, which in itself was high enough. As regards quinine, which was first used in 1949, the reduction of parasite rate from 5.19 in July to 4.04 in November is not itself significant, but there is no doubt that this drug exerted some control, for the parasite rate in the control group rose from 6.82 to 15.57 in the same period of time. The conclusion, confirmed statistically, was that chloroquine and camoquin prophylaxis offered the best protection. Of the two proguanil groups the bi-weekly regime (I) definitely gave better results than the weekly regime (II), though both were inferior to groups III and IV. The results obtained with bi-weekly quinine prophylaxis (V) were somewhat intermediate between the two proguanil regimes in respect of the parasite rate, but the difference was not statistically significant.

It has been mentioned that, in addition to the main camoquin group (III) receiving 0.2 g. of the basic drugs weekly, a subgroup was included in 1949 consisting of 50 subjects who were given 0.1 g. of camoquin (base) every week (IIIA). The parasite rates in the latter were similar to the main camoquin group (III). As the malaria incidence rate per 100 was 4.00 in group IIIA as compared with 3.12 in group III and 62.98 in group VI (control), it would appear that the effect of 0.1 g. of camoquin weekly is the same as that of 0.2 g. But, the number of subjects taken in group IIIA being very small, the similarity of its action with group III cannot be regarded as statistically significant. Nevertheless it shows that camoquin in such small dosage as 0.1 g. weekly can give considerable protection to persons exposed to malarial infection. It is possible, from the parasite rates in the control and treated groups, to calculate the degree of freedom from attacks afforded by each drug. Table IX gives the number of persons who would be freed from parasites by each of the drugs out of 100 who carry parasites in their blood.

The month of November has been chosen from each group, as this is the peak period for malaria.

TABLE IX.—*Percentage of Infected Persons Given Protection by Various Drugs*

	Nov., 1948	Nov., 1949
Proguanil (twice weekly) ..	88	82
,, (once weekly)	84	51
Camoquin (once weekly)	95	96
Chloroquine (once weekly) ..	93	100
Quinine (twice weekly)	—	74

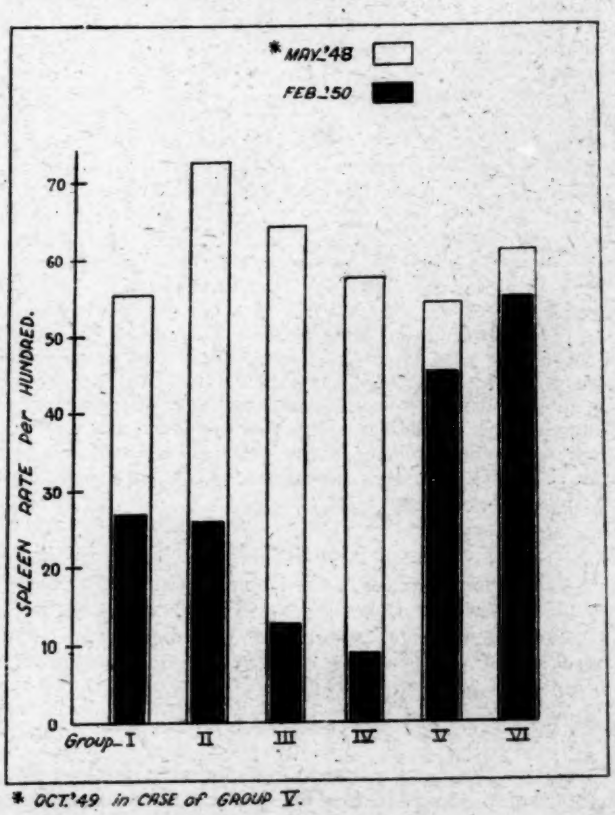
Spleen Rate

The reduction of the spleen rate is best seen from Table X.

TABLE X.—*Showing Effects on the Spleen Rate*

Group	May, 1948	Feb., 1949	Oct., 1949	Feb., 1950
	%	%	%	%
I	55·4	24·4	33·0	26·8
II	72·8	35·6	33·5	26·0
III	64·2	16·4	26·3	12·4
IV	57·7	18·2	25·7	8·8
V			53·4	43·1
VI	61·2	50·6	54·2	55·4

In keeping with their effects on the parasites, camoquin and chloroquine had considerably reduced the spleen rates—namely, to 12.4 and 8.8% respectively in February, 1950 (for convenience final spleen examination was made in February each year)—and these figures are lower than in the previous year. Curiously enough, though proguanil acted differently on the parasites according to the dosage scheme, the spleen rates in both groups were about the same—namely, 26% in February, 1950 (see Chart). Quinine was undoubtedly least effective in respect of the spleen rate, which was 43.1% in February, 1950, the initial rate being 53.4%. This would throw doubt on the efficacy of quinine prophylaxis in spite of its effect on the parasite rate. The control group, in accordance with our expectations, showed a persistently high rate, never falling below 50%.



* OCT.'49 in CASE of GROUP V.

To arrive at a proper evaluation of the drugs so far as the splenic enlargement is concerned, a statistical analysis was made of those subjects who had an enlarged spleen at the beginning of the experiment and those who had no such enlargement. The results in the former are similar to the overall figures shown above. In the latter, whose spleen was initially not palpable, all the treated groups showed prevention of splenic enlargement in varying degrees (see Table XI).

TABLE XI.—*Showing the Effect of the Drugs on the Spleen of Patients who had no Initial Splenic Enlargement*

Group	1948–9 Experiment		1949–50 Experiment	
	No. of Cases with No Palpable Spleen in May, 1948	Percentage Showing Enlargement in Feb., 1949	No. of Cases with No Palpable Spleen in Oct., 1949	Percentage Showing Enlargement in Feb., 1950
I	73	15	117	11·1
II	32	12	130	8·5
III	47	0	85	4·7
IV	31	0	90	1·1
V	—	—	68	6·3
VI	56	27	59	27·1

All the treated groups show significantly lower spleen rates compared with the control, in which 27% developed splenic enlargement after the transmission season. It was striking that in 1948–9 the spleen was not palpably enlarged at the end of the experiment in any of those subjects in the camoquin (III) and chloroquine (IV) groups who had not shown it at the beginning. In 1949–50 the lowest spleen rate was recorded in group IV, and is significantly less than all the other groups except III, which occupies an intermediate position between group IV and other treated groups. It may therefore be concluded that all the prophylactic regimes were effective in preventing splenic enlargement, chloroquine being most valuable in this respect.

Malaria Incidence

The data for malaria incidence during the prophylactic period were more accurately collected in the second experiment. Nevertheless they should be regarded as only approximate, because there were difficulties in obtaining correct information from the villagers. The incidence rate of malaria in those who were under prophylactic treatment was 21.54% with bi-weekly proguanil, 12.28% with weekly proguanil, 3.12% with camoquin, 2.27% with chloroquine, and 26.1% with quinine, as compared with 62.98% in the control group. It should be mentioned that only parasite-positive cases have been taken in the above analysis, and a person suffering more than once has been counted as one.

We might say that all the treatments were effective in reducing the incidence rate in so far as the rates recorded for these were significantly lower than that of the control group. Group III and group IV treatments were definitely better than all the others. There was no statistical evidence of difference amongst the other treated groups (I, II, and V). The higher rates in groups I and V may have been partly due to the method of collecting the data. These groups were paid two visits a week as compared with one visit in the other groups. This has undoubtedly inflated the figures in groups I and V to some extent. But, even taking this fact into consideration, camoquin and chloroquine show the best results in the prevention of malaria.

Conclusion

As in chemotherapy, so in chemoprophylaxis, chloroquine (base, 0.25 g. weekly) and camoquin (base, 0.2 g. weekly) have proved superior to proguanil (salt, 0.3 g. weekly or 0.1 g. bi-weekly). They afforded high protection and reduced splenomegaly, thereby improving the general health of the population and increasing the working capacity.

In spite of the fact that the people were living in poor economic conditions, and in the absence of any other antimalarial measures, there was marked reduction in the incidence of malaria, which varied according to the drugs used. Until anti-mosquito measures are possible chemoprophylaxis should have an important place in the suppression of malarial fever. It causes no inconvenience—a dose once or twice a week is enough, and it need not be costly. What is wanted is malaria discipline, but, once impressed, the villagers are willing to co-operate.

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ATYPICAL ABDOMINAL TUBERCULOSIS WITH HAEMATOLOGICAL MANIFESTATIONS

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Enlargement of the liver and spleen is an uncommon mode of presentation of abdominal tuberculosis. The four cases reported below illustrate the clinical appearance of this condition and, in addition, demonstrate the association of blood disorders with hepato-splenic tuberculosis.

Case 1

A woman aged 69 had had enlarged lymph nodes excised from her neck at the age of 6 years and a tuberculous right axillary lymph node removed when aged 36. For one year she had suffered from lassitude, haemorrhoids, and an uncomfortable swelling of the abdomen. The cardiovascular, respiratory, and nervous systems were normal. The spleen was hard, painless, and enlarged almost to the umbilicus, with a firm raised swelling 2½ by 1¾ in. (6.4 by 4.4 cm.) in size palpable on its surface. The liver was enlarged 1–2 in. (2.5–5 cm.) below the costal margin. She was afebrile and of a steady weight. A blood count on admission showed: Hb, 63% (9.1 g.%); red cells, 4,500,000 per c.mm.; white cells, 30,000 per c.mm. (neutrophils 86%, lymphocytes 4%, monocytes 3%, eosinophils 1%, metamyelocytes 2%, myelocytes 4%); platelets, 320,000 per c.mm. The blood film revealed hypochromia, microcytosis, and anisocytosis. The sternal marrow gave a total nucleated cell count of 200,000 per c.mm. (myeloblasts 3%, premyelocytes 2%, myelocytes 32%, metamyelocytes 10%, polymorphonuclears 38%, lymphocytes 1.5%, monocytes 0.7%). The myeloid/erythroid ratio was 9:1. These figures supported the clinical diagnosis of chronic myeloid leukaemia. After a course of deep *x*-ray therapy to the spleen her leucocyte count was 13,500 per c.mm., but rose subsequently to 28,000–50,000 per c.mm.

Six months later the patient was readmitted with severe pain in the left loin. She was ill, had lost 6 lb. (2.7 kg.) in weight, and ran a fever up to 102° F. (38.9° C.). The spleen reached beyond the umbilicus and was very tender. The liver was enlarged four fingerbreadths below the right costal margin. A blood count showed no anaemia. The leucocyte count was 15,900 per c.mm. (neutrophils 94%, lymphocytes 2%, monocytes 2%, eosinophils 2%). One week after admission ascites developed and a left pleural effusion collected shortly before her death.

Post-mortem Examination

The myocardium was pale and fatty. The left pleural space contained 2½ pints (1.4 litres) of yellow fluid, with some collapse of the lower lobe of the lung, roughening of the pleural surface, and slender fresh adhesions over the upper lobe. The right lung showed similar but less marked changes. No tuberculosis was found in either lung or in the mediastinal and cervical lymph nodes. The peritoneal cavity contained 7 pints (4 litres) of yellow fluid. The peritoneum and omentum were thickened and studded with white tubercles, chiefly small and discrete but some confluent, and most numerous in the omentum and the visceral peritoneum of the small gut. There were many peritoneal adhesions. The interior of the stomach and intestines appeared normal.

The spleen weighed 52 oz. (1.5 kg.), and on its anterior surface close to the tip was a circular mass 2 in. (5 cm.) in diameter, slightly raised above the surface, consisting of caseous material sharply demarcated by a fibrous capsule. The splenic pulp was soft and the follicular pattern could not be made out. The liver was considerably enlarged and on section was congested and fatty; the gall-bladder and bile ducts were normal. There were several caseous lymph nodes up to ¾ in. (1.9 cm.) in diameter grouped around the coeliac axis. The kidneys, suprarenals, and pelvic organs were normal. On splitting the right femur the marrow was seen to be pale pink in colour and soft in consistence, and it extended to the lower end of the bone.

Microscopical Examination.—The omentum contained many tuberculous giant-cell systems, some with caseous centres; occasional tubercle bacilli were found in them. The abdominal lymph nodes contained similar tubercles. In addition, one node contained a large caseous area surrounded by a hyaline fibrous capsule which showed early calcification. There was chronic venous congestion of the liver, which was infiltrated by a moderate number of miliary tubercles consisting of groups of epithelioid cells only, but containing occasional tubercle bacilli. The large mass in the spleen consisted of a structureless granular centre surrounded by a hyaline fibrous capsule. No organisms were found in it. The pulp of the spleen was congested, with hyperplasia of the sinus endothelium and many collections of epithelioid cells. No tubercles were seen in the substance of the lung, but some were present in the pleura. The bone marrow was vascular, few bone trabeculae remaining, and it contained tubercles similar to those in the liver. Haemopoietic cells were reduced in number, most of the cells present being reticulo-endothelial in type, resembling epithelioid rather than primitive myeloid cells.

Case 2

A man aged 67 had suffered from rheumatic fever when 14 years old; otherwise his health had been excellent. Early in 1949 he was admitted to hospital with congestive heart failure and auricular fibrillation. The spleen was enlarged and the liver palpable. He was anaemic (Hb, 46%; red cells, 3,800,000 per c.mm.) and had a leucocytosis of 22,000 per c.mm. (polymorphonuclears 80%). His heart failure and anaemia responded to treatment. By July, 1949, he had become plethoric and a blood count showed: Hb, 130%; red cells, 6,400,000 per c.mm.; white cells, 17,400 per c.mm. Venesection was performed repeatedly.

In February, 1950, he suffered again from congestive heart failure and after treatment was transferred to the Middlesex Hospital for radiotherapy for the polycythaemia. He had lost 14 lb. (6.4 kg.) in weight, looked ill, and had a pyrexia of 98–100° F. (36.7–37.8° C.). The chest was normal on both clinical and radiological examination. The heart was normal apart from auricular fibrillation and a blowing apical systolic murmur. The spleen, firm and slightly tender, was enlarged almost to the umbilicus, and the liver was palpable three fingerbreadths below the costal margin. Ascites was present. A blood count showed: Hb, 103%; red cells, 6,180,000 per c.mm.; white cells, 15,600 per c.mm. (86% polymorphonuclears); reticulocytes, 1.4%; platelets, 600,000 per c.mm. The sternal marrow gave a total nucleated cell count of 49,000 per c.mm. (myeloblasts 0.6%, premyelocytes 3.3%, myelocytes 6%, metamyelocytes 5%, polymorphonuclears 62.3%, lymphocytes 3%, monocytes 7.3%, plasma cells 0.6%). The myeloid/erythroid ratio was 7:1. The erythroid series was within normal limits and there was an increased number of megakaryocytes. He was thought to suffer from a myeloid leukaemic termination of polycythaemia and was given a diagnostic course of *x*-ray therapy (800 r) to the spleen, without effect upon the leucocytosis, which continued unchanged until his death.

Post-mortem Examination

The heart was enlarged—18 oz. (510 g.)—from hypertrophy of the left ventricle, but was otherwise normal. Both lungs were congested and oedematous, with bilateral pleural effusions. No tuberculous lesions were detected in either lung. The hilar lymph nodes were normal. The peritoneal cavity contained 9 pints (5.1 litres) of blood-stained purulent fluid and there was marked thickening of the peritoneal surfaces, with widespread firm adhesions. The stomach and intestines were normal. The liver weighed 70 oz. (2 kg.) and its capsule was thickened; on section, it was congested and showed diffusely distributed white deposits of miliary size. The spleen weighed 50 oz. (1.4 kg.) and many nodules varying in size from ¼ to ½ in. (0.3 to 1.25 cm.) were found in its substance. Most of the nodules were firm, but some were soft and caseous in their centres. The intervening splenic pulp was greyish red in colour and soft. Both kidneys contained simple cysts. The suprarenals, pancreas, and pelvic organs were normal. The abdominal lymph nodes along the aorta and at the root of the mesentery were enlarged, and on section areas of caseation were seen. A film of the peritoneal fluid stained by Gram's method showed numerous pus cells with profuse Gram-positive cocci and Gram-negative bacilli.

Microscopical sections of the abdominal lymph nodes showed numerous tuberculous giant-cell systems with areas of caseous necrosis containing scanty tubercle bacilli. Sections of the spleen showed considerably larger areas of caseation with extensive fibrosis of some of the lesions, but less granulomatous reaction and no tubercle bacilli. In the liver, miliary tubercles were abundant, with very occasional tubercle bacilli in them. The lungs showed congestion and oedema but no tuberculosis.

Case 3

A man aged 41 complained of lassitude and of pains in the joints for eight days. For five days he had noticed a rash on his skin, initially on the shins but later involving the whole of his body. He was pale and pyrexial—97–99.6° F. (36.1–37.6° C.). There were no abnormal physical signs, apart from a palpable spleen tip on full inspiration and a widespread skin rash. The rash was macular and ecchymotic, the majority of lesions being surmounted by small pustules. The rash did not fade on pressure, was not tender and was most pronounced on the legs. Hess's test was positive.

A blood count on June 19, 1945, showed: Hb, 49% (7.1 g.%); white cells, 2,600 per c.mm. (polymorphonuclears 33%, lymphocytes 63%, monocytes 3%, eosinophils 1%);

platelets, 350,000 per c.mm. A radiograph of the chest was normal. Serial blood counts showed that the anaemia and leucopenia persisted in the range: Hb, 33–49%; red cells, 1,600,000–2,600,000 per c.mm.; and white cells, 1,400–3,700 per c.mm., with an absolute neutropenia and relative lymphocytosis. The sternal marrow gave a total nucleated cell count of 25,000 per c.mm. (polymorphs 11%, metamyelocytes 4%, myelocytes 4%, premyelocytes 2%, myeloblasts 1%, lymphocytes 28%, monocytes 1%, late normoblasts 47%, intermediate normoblasts 2%). The myeloid/erythroid ratio was 0.5:1. A diagnosis was not made; the illness progressed steadily, with increasing fever, until the patient died one month after the onset of his symptoms. During the last week of life the spleen became impalpable, although coincidentally the liver enlarged and became tender on palpation.

Post-mortem Examination

Both pleural spaces contained 5 oz. (140 ml.) of yellow fluid. The lungs were voluminous, both lower lobes being solidified by coagulated oedema fluid, with areas suggesting infection of this jelly-like material. The upper lobes were emphysematous, congested, and oedematous. The hilar glands were enlarged and soft. There were no adhesions or free fluid in the peritoneal cavity. The stomach and intestines were normal. The spleen weighed 28 oz. (795 g.) and was purple in colour. No Malpighian bodies could be identified, but throughout the pulp were many nodules up to ¼ in. (0.3 cm.) in diameter, firm, and golden yellow in colour. The liver weighed 72 oz. (2 kg.); the left lobe was represented by fibrous tissue, but the right lobe was enlarged to the iliac fossa. On section there was pronounced mottling, suggesting alternating areas of congestion and fatty change; the gall-bladder and bile ducts were normal. A mass of soft swollen lymph nodes was seen in the upper part of the abdomen around the coeliac axis, individual glands being about ½ in. (1.25 cm.) in diameter. There was a single large calcified gland in the ileo-caecal mesentery. The other abdominal organs were normal. When the sternum was split it was found to contain red marrow; there was red marrow in the neck and upper third of the shaft of the left femur.

Microscopical Examination.—The abdominal lymph nodes, liver, and spleen contained areas of caseous necrosis surrounded by radially arranged cells resembling fibroblasts and by lymphocytes. No giant cells or typical epithelioid cells were seen, but very large numbers of acid-fast bacilli were found. The bone marrow was vascular, but haemopoietic cells were scanty and were surrounded by a loose fibroblastic tissue in which were numerous scattered, minute areas of necrosis. Although tubercle bacilli were absent, the lesions were histologically similar to those seen in the liver, spleen, and lymph nodes.

Case 4

A woman aged 60 complained of a goitre of recent onset and of excessive bruising for some years. Her spleen was palpably enlarged. A blood examination showed: Hb, 96% (13.9 g.%); red cells, 5,200,000 per c.mm.; white cells, 7,300 per c.mm. (polymorphs 63%, lymphocytes 30%, monocytes 5%, eosinophils 2%); platelets, 40,000 per c.mm. (two weeks later they numbered 55,000 per c.mm.); bleeding time, 8½ minutes (method of Duke); coagulation time, 4½ minutes (method of Lee and White). Splenectomy was performed without difficulty and the liver appeared normal. Five days later a blood count showed: Hb, 81%; red cells, 4,400,000 per c.mm.; white cells, 18,500 per c.mm. (polymorphs 85%, lymphocytes 9%, monocytes 6%); platelets, 350,000 per c.mm. The patient has remained well and entirely free from purpura since the splenectomy. The spleen was normal in size and weighed 3½ oz. (100 g.). It was firm but showed no abnormality on its cut surface. Microscopically there was some congestion and fibrosis of the pulp. There were occasional typical small tubercles with caseous centres throughout the organ.

Discussion

This type of abdominal tuberculosis probably originated in the para-aortic lymph nodes which had been involved in a lymphatic spread of infection from either a mesenteric or an intrathoracic tuberculous gland. The erosion of a caseous para-aortic node into a visceral branch of the abdominal aorta would disseminate the disease to the liver and spleen and to the intestines. The miliary tubercles in the bone marrow (Cases 1 and 3) cannot be regarded as the result of a blood-borne spread of the disease from the liver because of the absence of similar pulmonary lesions (apart from a few tubercles on the pleura in Case 1), and they remain unexplained.

Cases of this variety of abdominal tuberculosis have been reported under many titles (Winternitz, 1912; Fittipaldi, 1938), the most satisfactory being "atypical abdominal tuberculosis," suggested by Blair and Pagel (1947) in describing four unusual pathological types of tuberculosis of the abdomen. Both sexes may be affected at any age, and, unlike the classical forms of the infection, this atypical disease occurs not infrequently in old people, in whom tuberculosis may easily be disregarded as a cause of hepato-splenomegaly.

The disease has usually begun insidiously, most patients complaining of upper abdominal discomfort and swelling, lassitude, and malaise. Marked loss of weight and fever above 100° F. (37.8° C.) were uncommon. In a few cases a blood disorder has been the presenting feature, and in a minority the disease ran the rapid course of an abdominal tuberculous septicaemia (Ball *et al.*, 1951). Haematemesis has been recorded rarely as an initial symptom (Engelbreth-Holm, 1938; Howells, 1939). The spleen usually reached to, or even beyond, the umbilicus, and was firm, smooth, and often tender, but pain was caused only by infarction. The liver was moderately enlarged, smooth, and slightly tender in most cases. Ascites has been recorded.

When the cause of the hepato-splenomegaly was diagnosed before operation or death it had been suggested by the finding of active extra-abdominal tuberculosis, such as tuberculous lymphadenopathy (Hickling, 1938; Coffee and Lipton, 1943), bone and joint tuberculosis (Konstam, 1949), or active pulmonary disease.

Investigations in this disease have been singularly unhelpful. The Mantoux reaction has been of little assistance (Dietz, 1946). Radiographs of the abdomen may assist diagnosis by showing calcification in the spleen (Shands, 1933; Moorman, 1937), liver and spleen (Konstam, 1949; Astley and Harrison, 1949), or spleen and mesenteric glands (Solomon and Doran, 1939). Calcification in the lesions has been so uncommon that this method of investigation cannot be relied upon always to yield positive information.

There seems to be no certain method of distinguishing atypical abdominal tuberculosis from the many diseases producing a similar clinical appearance, apart from direct inspection of the abdominal contents. Coyon *et al.* (1927) performed splenic puncture and recovered tubercle bacilli from the aspirated material by guinea-pig inoculation. Liver puncture biopsy could perhaps be used with less risk (Graddock and Meredith, 1949).

The haemocytopenias associated with tuberculosis of the spleen have been attributed either to splenic or to bone-marrow tuberculosis. Engelbreth-Holm (1938) suggested that the infected spleen exercised an excessive control upon the emission of blood cells from the bone marrow, and Howells (1939), Dietz (1946), and Meredith *et al.* (1949) reported cases in which a leucopenia was corrected after removal of a tuberculous spleen. Solomon and Doran (1939) and Weiner and Carter (1941) recorded the cure of thrombocytopenic purpura in the same manner. Ball *et al.* (1951) ascribed the leucopenia of their cases of tuberculous septicaemia, and Gouley *et al.* (1949) the thrombocytopenia of their case of purpura and tuberculosis, to the tuberculous foci found in the bone marrow.

The return of the blood cell content to normal after splenectomy may be best explained by assuming hypersplenism, and not marrow tuberculosis, to be the cause of the haemocytopenias; hypersplenism may be excluded only if the blood count fails to respond to splenectomy. Although Ball *et al.* (1951) found marrow aplasia by sternal puncture in one of their cases, we obtained a normal marrow picture in our Case 3 with leucopenia, and the marrow was hyperplastic in the thrombocytopenic case of Gouley *et al.* (1949). The last finding is usual in cases of hypersplenism. Marrow tuberculosis is not always associated with a leucopenia, and in Case 1 there was in fact a leukaemoid reaction without anaemia.

The association of leukaemia and tuberculosis is rare, but a leukaemoid blood reaction may occur in the presence of tuberculosis. If the infection causes splenomegaly the simulation of true leukaemia may be perfect, the correct diagnosis being obtained only from a biopsy of the liver or spleen. When the tuberculosis is apparently confined to the abdomen its presence may not even be considered. Similarly, patients suffering from hepato-splenic tuberculosis and polycythaemia vera commonly present with no indication of abdominal tuberculosis. The polycythaemia in such cases was attributed to the splenic tuberculosis by Fitzpatrick and Schwartz (1949) when they reviewed the 36 recorded cases. Splenectomy has not been found to reduce the red blood cell count in these patients, and in Guild and Robson's (1950) case both irradiation of the spleen and its subsequent removal increased the severity of the polycythaemia. The evidence available does not confirm a causal relationship between splenic tuberculosis and polycythaemia.

Atypical abdominal tuberculosis has very rarely been treated with the correct diagnosis previously made. Splenectomy was advised by Winternitz (1912) in order to prevent a spread of the infection from the spleen, but it is improbable that the spleen is the most important focus of the disease, and, in fact, the tuberculosis may progress despite this operation (Frank, 1939). Splenectomy may become necessary, however, to relieve abdominal pressure symptoms or to correct a haemocytopenia.

Streptomycin has been used only twice in the treatment of hepatic or hepato-splenic tuberculosis (Guild and Robson, 1950; Melville, 1951). The results obtained were satisfactory, and at present it seems to be the treatment of choice for this condition.

Summary

Four cases of atypical abdominal tuberculosis are reported. Post-mortem examinations were made in three cases, all of which demonstrated tuberculosis of abdominal lymph nodes, liver, and spleen. Two of these cases also had miliary tuberculosis of the bone marrow.

One patient showed a leukaemoid reaction; another appeared to have suffered from polycythaemia; a third, whose illness was rapidly fatal, had a profound neutropenia and anaemia. The last case presented with thrombocytopenia. The relation of these blood disorders to the abdominal tuberculosis is considered.

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X-RAY APPEARANCES IN ASTHMA

A STUDY OF 200 CASES

BY

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The object of this investigation was to review the *x*-ray appearances in a series of patients suffering from asthma, together with the clinical findings in the same subjects, in order to find out if *x*-ray appearances could be correlated with clinical types, and to see in what proportion of cases complications occur.

Previous reviews of radiological findings in asthma—for example, Lapage (1922), Manges and Hawley (1927), Bray (1930)—are remarkable for the wide variety of terms used and for the comparatively few films which were regarded as normal. Little effort was apparently made to recognize emphysema, which we know clinically to be such an important and common complication, and segmental collapse was either not seen or not recognized at all.

Present Series

This series consists of 200 cases of bronchial asthma investigated at an allergy clinic, unselected in any way except that they were divided into two groups, the first consisting of 100 children aged from 14 months to 12 years, the second of 100 adults from 13 to 65 years. Such a division was found convenient, not because I consider that there is any fundamental difference between asthma in childhood and asthma in adult life, but because it is easier to compare films of similar-sized chests, and also because obviously the average duration of the disease will be longer in the older age group.

Table I shows the distribution between the sexes, the family history of allergy, and the average duration of the disease. There is little need to comment on these figures,

TABLE I.—*Sex Incidence, Family History, and Average Duration of Disease*

	Children 1–12 Years	Adults 13–65 Years
Total No. of cases	100	100
Males	66	50
Females	34	50
Positive family history of allergy	66	58
Negative ,, ,, ,,	27	26
Family history doubtful or not available	7	16
Average duration of disease	3 yrs. 10 mths.	11 yrs. 10 mths.

which show the usual preponderance of males over females among the children, and the large proportion with a positive family history of allergy (including asthma, hay-fever, chronic urticaria or dermatoses of allergic type, and migraine). They differ in no important respect from the many other similar series which have been published.

Aetiology

With regard to aetiology we find ourselves on very controversial ground in the present state of our knowledge. The classification adopted is one which is thought likely to be acceptable to a majority of students of asthma. While it is true that often more than one aetiological factor is operative, most cases fall into the broad groups set out in Table II: (*a*) "extrinsic" allergy—that is, hypersensitivity to specific inhaled or ingested allergens, giving rise to excessive antigen-antibody reactions; (*b*) "intrinsic" allergy, or hypersensitivity to invading micro-organisms or their products in the respiratory tract (this type is sometimes called infective asthma); (*c*) a combination of extrinsic and intrinsic allergy; (*d*) a group of cases in which an aetiological diagnosis was not made. Psychogenic factors and peripheral irritation are recognized as being important, but are regarded as being subsidiary or reinforcing. The relationship to endocrine activity is still too obscure to be useful from a classification point of view.

TABLE II.—*Aetiology*

	Children	Adults
(*a*) Extrinsic allergy	42	38
(*b*) Intrinsic allergy	15	17
(*c*) Combined	40	31
(*d*) Cause not definitely assigned	3	14

The diagnosis of infective asthma was made on clinical grounds: history, physical examination, pus in sputum or nasal discharge; and specialized rhinological examination. Laboratory help in the form of sputum examinations, blood counts, and sedimentation rates was sought in those cases where it was considered necessary. No single test was found to be reliable enough to make a diagnosis of bacterial allergy without support. The sedimentation rate, though increased when infection is active, gives no help in those cases of asthma caused by infrequent acute respiratory infections, where investigation is carried out in the free interval. Blood eosinophil counts were very variable, sometimes rising to 25% or more, and did not seem to bear any direct relation to the type of case under investigation.

Sinus Radiographs

Sinus radiographs showed, rather unexpectedly, a higher proportion of abnormalities in the children (62%) than in the adults (54%) (Table III). These figures compare closely with those of Unger (1945), who analyses nine reports of the incidence of sinus disease in asthma, giving an average of 60.4%, with a 26–82% variation.

TABLE III.—*Abnormalities Shown by Sinus Radiography*

	Children	Adults
Minor changes (slight mucosal thickening, etc.)	19	18
Marked changes (complete opacity, gross mucosal thickening, etc.)	43	36
No abnormality	38	46

It appears to be true that many "normal"—that is, symptom-free—individuals show opacities or mucosal thickening on sinus radiographs; Kern and Schenck (1929) found as many as 72% in 50 non-asthmatic controls. If we are to accept the work of Grove and Cooke (1933), these changes, which only in acute exacerbations become suppurative, are always caused by an infection which, in certain subjects, could at least theoretically lead to bacterial sensitization with resultant asthma. There is still, however, considerable lack of uniformity of opinion on the significance of these findings, and until there is more certainty I have tended to adopt a conservative attitude, and an abnormal sinus radiograph without other clinical evidence of infection has not been deemed sufficient to place the case in the infective groups.

Chest Radiographs

From the point of view of radiological appearances the cases seemed to fall naturally into the groups shown in Tables IV and V. A large number appeared to be within normal limits; others were normal apart from varying degrees of emphysema; another group, including some of the emphysematous ones, had markedly increased hilar shadows, with or without calcification; while a much smaller group had other important abnormalities.

Minor abnormalities, such as congenital malformations of the ribs, small diaphragmatic adhesions, small calcified lesions in the lung fields, and so on, were not taken into account, nor were the enlarged heart shadows of the occasional adult with coincidental hypertension.

TABLE IV.—*Chest Radiographs in 100 Children*

	No. of Cases	Infective	Non-infective	Average Duration
No abnormality	57	24	33	2 yrs. 11 mths.
Emphysema only	22	16	6	5 yrs. 9 mths.
Emphysema plus increased hilar shadows	6	5	1	
Increased hilar shadows	11	7	4	
Other important abnormality (4 cases):				
Segmental collapse	4	3	1	

TABLE V.—*Chest Radiographs in 100 Adults*

	No. of Cases	Infective	Non-infective	Average Duration
No abnormality	30	9	21	9 yrs. 6 mths.
Emphysema only	35	14	21	12 yrs. 1 mth.
Emphysema plus increased hilar shadows	11	8	3	
Increased hilar shadows	14	10	4	
Other important abnormality (10 cases):				
Segmental collapse	4	2	2	
Pulmonary tuberculosis	3	3	0	
Miscellaneous	3	3	0	

For the purpose of comparing the *x*-ray findings with clinical types it was found most convenient to divide the latter quite simply into infective and non-infective cases. The infective group consisted of those with "intrinsic" allergy (*b*) and the "combined" type (*c*) in Table II; the non-infective comprised the other two types, (*a*) and (*d*) in Table II.

Emphysema

It is important, from the point of view of prognosis, to distinguish between irreversible chronic "hypertrophic" pulmonary emphysema and pulmonary distension due to an asthmatic attack. In order to do this it may be necessary to repeat the physical and *x*-ray examination, and the measurement of vital capacity, at a time when the patient is "at his best"; this has been done in some cases in the series under review. Considerable help in the diagnosis can be obtained by taking films in full inspiration and full expiration and comparing the difference in translucency, density of the broncho-vascular markings, height of the diaphragm, etc., in the two films. Comparison between a film taken in expiration with that of a normal control of similar age and build has also been of assistance in some cases. In spite of these devices, however, there is probably a margin of error, especially in the case of the children, where scope for examination is of necessity somewhat limited.

Tables IV and V show that emphysema, as we would expect, was found in a greater number of adults than children (46 to 28). In both children and adults the average

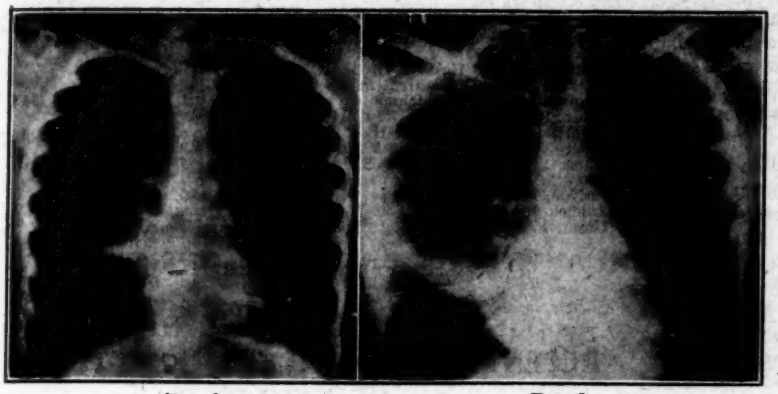

FIG. 1. FIG. 2.

FIG. 1.—Segmental collapse, middle lobe, in girl aged 11. Fig. 2.—Segmental collapse, middle lobe, in man aged 36.

duration of the disease was longer in those with emphysema. In the adults the distribution of emphysema between infective and non-infective cases was about equal (22 to 24), but in the children the infective type largely predominated (21 to 7). This might be interpreted as indicating either that infective asthma is more severe in children or that the chronic cough, which many of the infective cases have, produces that added strain on the alveolar walls which determines the onset of emphysema. In the case of adults, the element of chronicity alone seems to be of importance.

Increased Hilar Shadows

It is assumed that, for all practical purposes, these indicate enlarged tracheo-bronchial glands, which again argues past or present lung infection. Some of these were undoubtedly due to a primary tuberculous infection in early childhood, others to acute or chronic non-tuberculous bronchial or pulmonary infection. It is therefore not surprising to find that in this group the infective cases largely predominate (30 infective to 12 non-infective in the whole series).

Bronchiectasis

This has not been taken into account here. Without doing routine bronchograms it would obviously be impossible to say what number had developed this complication, and bronchograms have been done in only a small number of cases. Of the whole 200, including those with phthisis, only nine had any haemoptysis, and this was usually slight, while clubbing of the fingers was seen in only two. Bullen (1933) found bronchiectasis in 7.75% of asthmatics, and Chapman and Hoskins (1941) state that when it occurs it is usually of the cylindrical type. Only one of our bronchograms showed definite saccular bronchiectasis, and my impression is that permanent bronchiectasis of clinical significance is not a common complication of asthma.

"Thymic" Asthma

Pressure on the trachea by an enlarged thymus is sometimes given as a cause of asthma—like dyspnoea in infants and young children. A lookout was kept for any radiological evidence of enlarged thymus, but it did not appear. It must be uncommon, and hardly a force to be reckoned with from the point of view of differential diagnosis.

Segmental Collapse

This was seen in eight cases (four children and four adults). Among the children it affected the middle lobe in three cases and the left lower lobe in one case. The latter took over a month to re-expand, whereas in the others re-expansion was rapid. In one case there was complete disappearance of the typical wedge-shaped shadow in a film taken 24 hours later (see Fig. 1). Of the four adults with segmental collapse the middle lobe was affected in three cases, and the lower part of the left upper lobe in the other. In all cases re-expansion was rapid (see Fig. 2).

It should be emphasized that all these patients were investigated as out-patients, and that none was acutely ill at the time. Except for the child with left lower lobe collapse, I do not think that it would have been possible to diagnose the condition without radiographs. The severity of the patient's asthma seemed to bear no relation to the presence of collapse. One man, who had been gravely ill with acute asthma as an in-patient, had a clear *x*-ray film when in hospital. When referred for investigation 10 days later as an out-patient, much improved, another *x*-ray film showed an area of collapse, which completely disappeared within the next week, without any noticeable change in his physical condition.

It seems probable that collapse, due presumably to the blocking of a smaller or larger tube by a mucous plug, is commoner in asthma than is generally realized, though all degrees of it, up to massive collapse of a whole lung, have been described by various writers—for example, Clarke (1930), Maxwell (1937), Friedman and Molony (1939).

Pulmonary Tuberculosis

There has been much speculation in the past about a possible relationship between pulmonary tuberculosis and asthma, but most of the available evidence suggests that the former occurs no more frequently in asthmatics than in the population as a whole. In the series under review no cases of active pulmonary tuberculosis were found among the children, but three adults, aged 29, 35, and 65 years, had the disease. All of these were asthmatics of long standing; two had positive family histories of allergy, and all had tubercle bacilli in the sputa. The incidence of 1.5% of phthisis in this series is probably higher than that in the total population, but the numbers involved are too small for any conclusion to be drawn from this.

Miscellaneous Abnormalities

Three cases come under this heading. The first was a woman of 60, with a lifelong history of asthma, whose radiograph showed part of her stomach to be above the

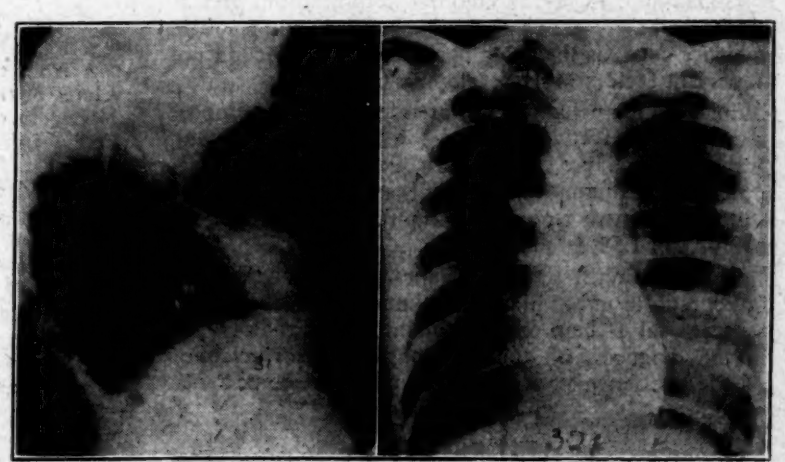

FIG. 3. FIG. 4.

FIG. 3.—Thoracic stomach. Woman aged 60. Lateral film. FIG. 4.—Dense opacity, left lower lobe. One of several opacities recurring in different situations.

diaphragm. There was an ulcer on this portion, from which she later had a large haematemesis. This condition had, of course, no relation to her asthma, but the case serves to illustrate how important coincidental conditions sometimes come to light in the course of a routine investigation (see Fig. 3).

The other two cases, both young adults with incessant asthma since infancy, showed recurrent evanescent shadows in different situations on their chest radiographs during a follow-up period of over four years. One patient subsequently twice developed pulmonary abscesses, which she spontaneously evacuated, and material sucked from the infected area through a bronchoscope grew a *Streptococcus viridans*. The other patient also at one time developed a small abscess cavity with a fluid level, which quickly disappeared spontaneously. In neither case did the blood eosinophils ever exceed 6% (see Fig. 4).

Transitory opacities seen in the chest radiographs of asthmatics, such as occurred in the last two cases, have been described by many authors—for example, Peshkin (1927) and Sédillot (1934). There has been considerable speculation about their nature, particularly whether they are caused by localized areas of infection or by eosinophilic infiltration. The character of these two cases suggests that infection is the cause in some of them.

Summary and Conclusions

A review of the radiological findings in 200 cases of asthma, 100 children and 100 adults, is presented, and an attempt made to correlate the *x*-ray appearances with clinical findings. The series consists of typical cases of asthma, seen as out-patients only.

Sinus radiographs show changes in over half the cases, there being a higher proportion with marked abnormality in the children than in the adults.

Chest radiographs, disregarding minor abnormalities, fall into five groups: normal, emphysema, emphysema and increased hilar shadows, increased hilar shadows, and other important abnormality. The last group includes cases of pulmonary tuberculosis, segmental collapse, and recurrent transient shadows believed to be due to localized areas of infection.

In attempting to distinguish between irreversible emphysema and pulmonary distension due to the bronchiolar obstruction of asthma, the value of radiographs taken in full inspiration and full expiration, and of comparing one taken in expiration with a normal control, is stressed.

Emphysema is the commonest complication, and is judged to be present in 28 children and 46 adults. The evidence suggests that both chronicity and infection are important factors in its development.

Enlarged hilar shadows are present in a higher proportion of the infective than of the non-infective cases. Segmental collapse, with subsequent satisfactory re-expansion, is present in 4%, and is seen in both infective and non-infective types. Active pulmonary tuberculosis is found in 1.5%.

In conclusion it should be pointed out that the chest radiograph in uncomplicated asthma is normal, but that a great deal of help can be obtained from radiography in the diagnosis of complications, in the elucidation of the aetiology, and in the discovery of coincidental conditions.

I should like to express my thanks to Drs. C. N. Pulvertaft and R. A. Ashwin, consultant radiologists to the County and City General Hospitals, York, whose co-operation and assistance with the radiological diagnosis have made this investigation possible.

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THE TREATMENT OF RECENT TRANSCERVICAL FRACTURES OF FEMUR

BY

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Much has been written on this subject during the past 20 years, and our only excuse for adding to the literature is that we have evolved a simple method of treating these injuries, the results of which seem to compare favourably with those of any other method so far described.

It is now generally agreed that the treatment of choice in transcervical fractures of the femur, particularly those of the adduction type, is some form of nailing operation, with or without a bone graft according to the nature and age of the fracture; and our treatment is based on the internal fixation operation originally described by Smith-Petersen *et al.* in 1931. During the past four years rather more than 100 such operations have been carried out, and we wish to describe the management and the results in a consecutive series of 100 cases in which the end-result is clear. The number of patients involved was 98, two of them having the second hip nailed a few months after the first. The great majority of them were women, the injury being much less common in men.

Selection and Management of Cases

Abduction fractures with impaction are excluded from this series, it being unnecessary to operate on most of them. Apart from these, all the cases admitted with adduction fractures of the femoral neck have been included, and were subjected to operation unless they were moribund or were suffering from advanced senile mental changes. Indeed, several cases from a neighbouring mental hospital have been successfully treated.

Unlike Bankart (1942), who advocated that few patients over the age of 80 should be operated upon, we have not made age alone a bar to operation. The average age in this series was 73, and the range extended from 44 to 93, 60% of them being in the age group 71–85.

On admission all patients are subjected to a full clinical examination and radiographs are taken of the injured hip to determine the nature of the fracture. The patient is then put to bed and a simple form of skin traction is applied to the injured leg by means of extension strapping applied below the knee. The usual weight employed is 9 lb. (4 kg.), which is connected to the strapping by means of a cord passing over a pulley attached to the lower bed-rail. This simple form of traction does not immobilize the

fracture, but it has the merit of preventing, or correcting, any gross shortening. It also steadies the limb, thus relieving the patient of a considerable amount of pain.

Should the general examination reveal the presence of moist sounds at the lung bases, penicillin is given in the form of its procaine salt, 300,000 units daily; and in all cases breathing exercises are begun under the direction of a physiotherapist. A simple explanation is also given of the patient's post-operative management, and foot drill is initiated. In most cases no other pre-operative measures are carried out, but should a patient be suffering from diabetes mellitus this is stabilized as rapidly as possible. None of the resuscitative measures described by some surgeons (Harmon, 1945), such as blood transfusion, have been found to be necessary. As soon as a suitable opportunity occurs the patient is operated upon, and this is usually carried out within a few days of the injury.

The Operation

Here again simplicity has been our keynote, and all direction-finding aids have been discarded except one—namely, the hinged gauge (London Splint Co.). All patients have been given a general anaesthetic, usually thiopentone, gas–oxygen, and "trilene," with D-tubocurarine or similar drug, and the operation is nearly always completed well within an hour.

A slightly modified fracture table is employed, a padded wooden platform being fitted in place of the usual small sacral rest. Beneath the platform is a slot into which cassettes can be inserted without disturbing the position of the patient.

The patient is placed upon the table and enough traction put on the uninjured limb to steady the pelvis. The injured limb is then manipulated by hand into a position of abduction and internal rotation and enough traction applied to render the limb just taut. In nearly all cases these simple manœuvres are sufficient to ensure full and accurate reduction of the fracture.

As Van Gorder (1948) and others have already mentioned, a bony spike attached to the inferior border of the femoral head may make accurate reduction difficult, and it may be shown that further manipulation is necessary after the initial *x*-ray films are developed.

Two portable *x*-ray units are then placed in position and the hinged gauge is attached to the front of the hip with strapping in such a position that the hinge lies just below the anterior-superior iliac spine; one limb lies in the groin crease and the other lies in the line of the femoral shaft. After the first films are developed, the accuracy of the reduction is checked, and from the superimposed image of the gauge in the antero-posterior film two points can be marked on the skin with methylene blue which, when joined, will show the correct line for the nail in the horizontal plane. The correct line for the nail in the vertical plane is taken as being parallel with the floor, with, if anything, a slight posterior tilt.

It has been our aim to insert the nail at a slightly more oblique angle to the shaft than the long axis of the femoral neck, as advocated by Bankart (1942), thus converting shearing forces at the fracture site, especially in those cases corresponding to Pauwel's (1935) group 3, to impacting forces. We also try to complete the operation with the nail lying slightly behind and below the long axis of the neck, and with its tip coming to rest just beneath the articular surface of the head. With the nail so placed, there is much less danger that it will cut out if the femoral head undergoes avascular necrosis or if the capital fragment is very small.

With these aims in mind the operation is proceeded with in the usual way, the guide-wire being inserted well into the head fragment to prevent rotation while the nail is being hammered in. We have no objection to the guide-wire perforating the articular cartilage of the head, but do not make a point of pushing it right through into the pelvis, thus completely transfixing the head, as described by Bankart. The guide-wire is of known length, and the correct size of nail can be determined by measuring the length of guide-wire protruding from the lateral cortex of the femur. The nail is hammered in over the wire, without the preliminary use of a starter. The wire is withdrawn, traction on the limb is slackened, and the fragments are impacted with a few blows from the mallet.

The wound is then closed, no additional measures, such as the insertion of cross-pins, being taken to prevent the nail from sliding out during convalescence. There are two reasons for omitting this step. The first is that if the nail should become loose enough to allow lateral extrusion the anchoring cross-pin will probably loosen also. The second is that complete prevention of lateral sliding is apt to cause slight separation of the bony fragments due to the bony absorption that occurs about any fracture during the early stages of healing, and therefore gives rise to delayed union or non-union.

Post-operative Care

Various methods of restricting external rotation of the injured limb after operation have been tried and discarded. As a routine measure we now use the abduction frame designed by McLean (1949). This frame prevents external rotation and adduction of the limb while permitting flexion and extension of the knee- and hip-joints. It also acts as a bed-cradle, thus relieving the legs of the weight of the bedclothes.

The day after operation active exercises under the direction of a physiotherapist are begun, all movements of the hip, knee, and ankle being permitted except external rotation and adduction of the hip-joint.

At the end of one month a radiograph of the injured hip is taken, and if the position of the nail and of the bony fragments has been maintained the patient is allowed up daily for non-weight-bearing exercises on crutches. Further *x*-ray films are taken at intervals of a month, and, provided that there is radiological evidence of bony union, graduated weight-bearing exercises are begun at the end of three months. If union has not occurred, or its degree is doubtful, weight-bearing is postponed until it is definitely present, and this may mean a delay of six months or more in some cases.

Provided home conditions are satisfactory and the general condition of the patients is good, they are discharged from hospital when they have learnt to manage crutches. Most of our cases, however, have remained in hospital for the full three months, principally because they lived alone.

Results of Treatment

In view of the fact that the nailing operation has been carried out in every case unless it was obvious that the patient was moribund on admission, we believe our results compare favourably with most of those published to date. A few surgeons have achieved a higher percentage of union, but they have usually been on a smaller series of cases and a more careful selection has been made, thus lessening the risk of failure.

In our series of 100 operations, union has been achieved in 75, with one death attributable to the operation. This death occurred in a woman, aged 85, 24 hours after operation. Altogether nine patients died while under treatment, but in eight death did not occur until several weeks or months after operation, and in none of them could the cause be related to the operation. The full results are summarized below.

No. of patients	98	
No. of operations	100	(bilateral in two patients, aged 66 and 78)
Average age	73	(range 44 - 93)
No. united	75	
No. ununited but ambulant	10	(7 with and 3 without callipers)
No. of nails removed	4	(1 had united)
Incidence of wound sepsis	Nil	
Deaths while under treatment	9	

Causes of death:

- 1 operative shock, aged 85
- 1 cerebral arteriosclerosis (senility), aged 81
- 2 myocardial degeneration, aged 80
- 1 pulmonary embolism, aged 74
- 1 acute gastro-enteritis and cardiac failure, aged 79
- 1 coronary thrombosis, aged 75
- 2 hypostatic pneumonia, aged 74 and 76.

Summary

A simple method of treating adduction fractures, and abduction fractures which have disimpacted, of the femoral neck is described. The results appear to be satisfactory according to modern standards. Bone grafting was not carried out in any case.

In those cases in which the nailing operation failed, further surgical intervention was not undertaken because of the age of the patients and their general condition.

We are indebted to Sister Pinfield, the sister of the ward in which most of these patients were treated; to our anaesthetist, Dr. R. E. Gibson; and to Miss Savin and her all-too-small band of physiotherapists for any success we may have achieved in the management of this series of fractures.

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ADDENDUM.—Since this paper was written one more case must be listed as a failure. Thus the percentage of successful cases in this series is 74.

THE KAHN TUBE TEST WITH DROPPING-PIPETTES

BY

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In recent years many laboratories have abandoned the Wassermann test and substituted the Kahn standard tube flocculation test as being superior to complement-fixation methods. The belief that the Kahn test gives more false positive results than the Wassermann has been seriously challenged by Berger and Sutherland (1944). But though the Kahn method is relatively simple, in performance it is exacting, especially in the measurement of small volumes of antigen in graduated pipettes. This disadvantage can be largely overcome, and the test set up more rapidly, by the use of pipettes standardized to deliver drops of known volume. Such pipettes have already been advocated in other serological tests for the diagnosis of syphilis—for example, in the Wassermann reaction (Donald, 1916), the sigma reaction (Dreyer and Ward, 1921), and in slide flocculation tests (Mazzini, 1942; Gradwohl, 1943; Harris *et al.*, 1948).

As regards the Kahn test, the volumes of reagents used are economical and the smallest practicable for volumetric work in test-tubes. Osmond (1940) used a dropping-pipette to deliver the standard 0.0125 ml. of antigen suspension. He recommended a pipette with a tip diameter equivalent to No. 54 on the Morse scale (1.397 mm., or 0.055 in.).

Two pipettes are described below—one for the delivery of 0.0125-ml. volumes of antigen, the other for 0.15-ml. volumes of the patient's serum.

Dropping-pipette for Antigen

30-cm. lengths of 7-mm. soft glass tubing are drawn to make two pipettes. The tip diameter is found by thrusting the capillary portion into the No. 55 Morse gauge hole (1.321 mm.) of a Starrett plate and cutting the tube at the point where it jams in the hole. When cut the capillary portion should be about 6 cm. long, with sides nearly parallel for the last 4 cm. The external diameter of the tip, which should be 1.30 mm. (0.051 in.), is checked by a micrometer screw gauge, making two measurements at right-angles to one another. It is useful at this stage to mark the capillary shaft with waterproof ink exactly 1 cm. from the tip, so that after cleaning, etc., pipettes with broken tips may be readily recognized and discarded.

The correct diameter (1.30 mm.) was arrived at as follows. A pipette was calibrated with mercury to contain 1 ml., and the weight of 1 ml. of antigen suspension was found to be 0.91 g. Weighed 0.91-g. amounts of the antigen suspensions were then drawn into dropping-pipettes of different tip diameter to determine which delivered 80 drops to the ml.—that is, 0.0125 ml. per drop. (A 1.397-mm. pipette (Osmond, 1940) was found to deliver 77 drops to the ml.)

This volume is delivered in one drop when the rate of dropping is one per second from a vertically held pipette. But even with care in maintaining an even rate of dropping there is some variation in the size of the drop. It was not possible, however, to minimize the error by delivering the same volume of liquid in a number of smaller drops. Thus to deliver two drops of half the required volume (0.00625 ml.) a tip diameter of 0.62 mm. was necessary, and capillary shafts of this size are too fragile for routine use.

Compared with 0.1-ml. *graduated* pipettes, marked to deliver 0.0125-ml. volumes, the dropping-pipette is much quicker and easier to use. In a two-tube test, one receiving one drop (0.0125-ml.) and the other two drops (0.025 ml.), it took about four minutes to dispense antigen suspension for 100 tests. With graduated pipettes the same operation took 22 minutes. The dropping-pipette technique is readily acquired by the laboratory technician, whereas the use of graduated pipettes demands more experience and entails much more eye strain.

Dropping-pipette for Patient's Serum

The Kahn standard test requires the delivery of 0.15-ml. volumes of serum. The weight of 1 ml. of a pool of five inactivated human sera proved to be 1.02 g. Of this pool 0.918-g. amounts (0.9 ml.—that is, six 0.15-ml. drops) were tested in pipettes of different tip diameters, with the following results:

Tip Diameter (mm.)	No. of Drops in 0·9 ml.	No. of Drops in 0·15 ml.
2·8	18	3
5·0	12	2
9·3	6	1

Only the results with pipettes delivering simple fractions of 0.15 ml. are cited above. The 2.8-mm. diameter was selected because in practice the variation in volume is less when the 0.15 ml. is delivered in three drops than in two or one.

With this 2.8-mm. pipette, delivering 0.15 ml. of serum in three drops (0.05 ml. of serum per drop) at the rate of one drop per second, 100 sera could be dispensed, each in three 0.15-ml. volumes and with a triple rinse of the pipette in saline for each serum, in 33 minutes. With a graduated 1-ml. pipette, similarly rinsed for each serum, the same operation took 45 minutes.

The Kahn Test with Dropping-pipettes

Apart from the saving of time and labour in the performance of the test, and the ease with which accurate dropping-pipettes can be constructed by a competent laboratory technician, the dropping-pipette technique permits a modification that is useful, especially when the test is done in hot climates. In the standard test the antigen suspension is dispensed first, and when large numbers of sera are to be tested there is a real risk of evaporation of the smallest dose (0.0125 ml.) of liquid. Serum is added to antigen, and not vice versa, presumably because the antigen pipette might

become contaminated with serum left on the upper part of the tube when graduated pipettes are used. With dropping-pipettes, on the other hand, there is no chance of such cross-contamination, and the bulkier serum volume, which is proportionately less susceptible to evaporation, can be dispensed first. It is, indeed, convenient to dispense the serum while the antigen suspension is "ripening."

There seems to be no good reason why this change in the order of adding reagents should not be made. In order to make sure that nothing goes wrong if Kahn's recommendations in this respect are not adhered to, 500 sera were tested both ways, 100 on each occasion, using the same bottle of antigen each time. The results, in which 60 of the sera were positive, agreed in every instance.

Another economy can be achieved by omitting the first of the three tubes used in the Kahn standard test (Osmond, 1940; Panton and Marrack, 1947). This tube contains the largest volume of antigen suspension (0.05 ml.), and its omission not only saves time and labour but results in a very real saving of antigen. The only advantage of this tube seems to be that its floccules, when present, are usually the most easily visible with the naked eye when the two other tubes have to be read with the aid of a magnifying glass. There is no great loss when that tube is omitted, because a magnifying lens has to be used in any case. The most useful magnifying glass for detecting small floccules is one that shows them in sharp focus when the lens mount is applied *in direct contact* with the tube. The Bausch and Lomb ×7 achromatic focusing magnifier (for photomicrography) satisfies this condition. A microscope eyepiece can be used if the top lens is removed and the observer's eye applied to the lower end. The Bausch and Lomb ×5 Huygenian eyepiece is satisfactory, because the Kahn tube can be held in contact with the end of the eyepiece tube, from which the top lens has been removed. Not all makes of eyepieces are suitable.

Summary and Conclusions

The performance of the Kahn standard test is greatly facilitated by the substitution of dropping-pipettes for graduated pipettes. Dropping-pipettes are easy to make and simple to use without eye strain.

A dropping-pipette with an external tip diameter of 1.3 mm. delivers the required standard 0.0125-ml. volume of Kahn antigen suspension when the rate of delivery is one drop per second. In routine tests antigen is dispensed in about one-fifth the time needed with graduated pipettes.

A dropping-pipette with an external tip diameter of 2.8 mm. delivers the required standard of 0.15-ml. volume of serum in three drops when the rate of delivery is one drop per second. It can be readily rinsed in saline for each serum. Compared with graduated pipettes, its use in dispensing serum makes routine tests about 30% quicker.

In the Kahn standard test, sera are dispensed *after* the antigen, and the small 0.0125-ml. volume of antigen may partly evaporate before serum is added. With the dropping technique the bulkier volume of serum, from which evaporation is proportionately less, may be dispensed first.

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Medical Memoranda

Hour-glass Bladder

The name hour-glass bladder seems familiar, but it is not mentioned in several standard textbooks consulted. Perhaps the apparent familiarity of the title is due to memories of hour-glass stomach. However, the following case seems worthy of record as an hour-glass bladder.

CASE REPORT

A spray painter aged 33 was seen at the West London Hospital on March 21, 1946. He had had cystitis, with difficulty of micturition, in 1942 and 1945, when cystoscopy, sulphanilamide, and prostatic massage figured in the treatment. He now again had had difficulty of micturition for nine months, with burning during the act, and slightly increased frequency (D/N=2–4 hours/0–1), but no haematuria. He also had a feeling that he was not emptying the bladder properly, and had occasionally noticed swelling of the abdomen during the past nine months, with some suprapubic tenderness, and nine months previously had had acute retention.

There was no venereal history or any evidence of stricture or enlarged prostate. The urine contained pus in fair amount, a few red cells, and many coliform bacilli. *Proteus vulgaris* was grown.

Plain *x*-ray films on March 28 and April 8 showed no stone shadow, but apparently a big bladder shadow that filled the pelvis. Intravenous urography on the latter date, while showing good bilateral renal excretion shadows in five minutes without renal or ureteric dilatation, also showed a big bladder shadow, filling the pelvis, even after micturition.

On April 4 cystoscopy revealed a bladder capacity of 3 pints (1.7 litres) and a well-marked narrow ridge, projecting forwards from the posterior wall, with the ureteric orifices situated laterally on the ridge. The blood urea was then 72 mg. per 100 ml. On April 11 the bladder was still up to the umbilicus after the withdrawal of 2 pints (1.1 litres) of residual urine. A $\frac{12}{12}$ English metal bougie was passed. The urine urea was 0.98%.

On admittance on April 12 the bladder, over which there was no tenderness, was found distended only half-way to the navel. Dr. Redvers Ironside found no organic signs referable to the nervous system or any clinical evidence of associated congenital abnormality.

On April 23, after a period of catheter drainage and bladder lavage, cystoscopy again showed a free interureteric bar, and cystotomy a large bladder with thickened and reddened mucosa lying convexly inwards in flabby folds.

A transverse fold, attached posteriorly, free anteriorly, and projecting forwards like a shelf, lay loosely across the bladder, with the right ureteric orifice identified and probed on it, and a very deep capacious proximal recess, bigger than a closed fist, and seemingly bigger than the distal division of the bladder.

The fleshy fold was held up and, $\frac{1}{2}$ in. (1.3 cm.) to the left of the right ureteric orifice, was cut antero-posteriorly in the middle line for about 2 in. (5 cm.), the cut not reaching to the bottom of the fold, yet entering a cavity—not the rectum, but presumably the recto-vesical interval.

The proximal mucosa was sewn to the distal mucosa by a continuous suture on the right and left of the V-shaped gap thus formed, the temptation to cut away the resulting triangular flaps being resisted because of the ureteric orifices on the free margin of the fold. The bladder and space of Retzius were drained by plain tubes.

Looking again at the intravenous urography films one detects, in the 30-minute film, some evidence of this curious division of the bladder cavity into two compartments.

On July 1 the blood urea was down to 48 mg. per 100 ml., and the residual urine to 9 oz. (255 ml.), the catheter urine showing a deposit of epithelial cells, a few leucocytes and red cells, triple phosphate crystals, and numerous Gram-

negative coliform bacilli, growing as *Proteus vulgaris*. On July 8 the residual urine, thick and purulent, was down to only 6½ oz. (185 ml.), while the deposit from the mid-stream urine contained a few pus cells and a few streptococci, growing poorly as non-haemolytic streptococci. The patient has not been subsequently seen, and cannot be traced.

As stated, the recess proximal to this extraordinary transverse fold, which is obviously congenital, and whose origin may be left to embryologists, seemed larger than the distal recess; and it appeared as if a collection of urine in the upper pocket might distend the fold downwards and so obstruct the internal urethral meatus. The median division of this fold would, it might be supposed, prevent this by allowing urine to flow freely from the upper to the lower pocket. That this reasoning is correct is suggested by the course of the case, mere median division of the fold being followed by a fall in the residual urine from 60 to 6½ oz. (1,704 to 185 ml.).

It would be interesting to know if others have met with similar cases.

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Blindness in Southern Nigeria

What are the causes of blindness in Southern Nigeria? Does blindness in this part of tropical Africa result mainly from tropical diseases, epidemic or endemic? As there were no reliable answers to these questions and as this subject is of considerable importance, an attempt was made to investigate and to record the immediate and remote causes of all cases of blindness seen at the Lagos Eye Clinic.

Harold Ridley (1945) has described an area in the Gold Coast where a considerable number of the inhabitants are blind from onchocerciasis, which is endemic in that district. No condition comparable to this has as yet been discovered in Nigeria. Trachoma is widespread and entropion from contraction of the lids has been reported to be very common in the Northern Territories of the Gold Coast and Northern Nigeria (Dr. Cave and Dr. Branch, personal communications). It was seen less often in cases from Southern Nigeria.

It has been said that a large proportion of the blindness in Nigeria is due to epidemics of smallpox. Occasionally, in cases of leucoma, the patient has stated that smallpox was the direct cause of the condition, but accurate information about the real number so affected is lacking, and there are no grounds for such a dogmatic statement. Tropical diseases undoubtedly increase the liability to blindness by lowering tissue resistance to infective processes, but it is not possible to assess the effects of malaria, helminthic disease, etc., which are commonly found coincidently with eye disease in Southern Nigeria.

RESULTS OF INVESTIGATION

The Lagos Eye Clinic deals with 7,000 new cases yearly and 20,000 attendances. From 1946 to 1949, inclusive, all cases of blindness attending the clinic were examined and the records kept. The standard of blindness adopted was visual acuity less than 3/60 Snellen. In a large number of cases it was not possible to do more than make a diagnosis of the condition present at the time of the examination. There were, for example, 29 persons totally blind with staphyloma, leucoma, or phthisis bulbi. When these patients were led into the clinic it was apparent that treatment could not improve their condition. In such cases it is not always advisable to ask questions about the origin of the condition. Almost all the cases recorded were from Southern Nigeria, being referred from district hospitals or coming of their own volition.

Total Blindness.—The accompanying Table shows that the commonest causes are cataract, glaucoma, and optic atrophy in that order of frequency. To the figure for cataract might be added the 11 cases blind from the operation for couching. So far as I am aware the fact that couching for cataract is being done in Nigeria has not hitherto been reported. It is probable that as the more orthodox operations are not available this ancient practice is widespread. From personal observations it seems that two types of operative procedure are practised: dislocation by a needle or thorn is sometimes employed, or manual dislocation by pressure with the fingers. So far as can be ascertained the native manipulators are all Hausa—that is, natives of Northern Nigeria. Acute glaucoma is rarely seen in Lagos. The cases recorded are all the end-result of the chronic simple type of symptomless glaucoma. It will be noted that a considerable proportion of the blindness could be prevented or cured. This investigation shows definitely that no single disease can be quoted as a main cause of blindness in Southern Nigeria.

Table of Blindness

Causes of Blindness	Blind in Both Eyes	Blind in One Eye
Leucoma, phthisis, staphyloma	29	213
Choroiditis	13	32
Cataract, senile	115	223
Cataract, congenital	20	19
Local infections	16	94
Traumatic	0	129
Glaucoma	72	49
Optic atrophy	44	39
Optic neuritis	1	0
Myopia	5	16
Avitaminosis	3	0
Trachoma	19	19
Iridocyclitis	2	90
Retinal detachment	3	9
Orbital tumours	0	2
Couching	11	13
Onchocerciasis	1	1
Interstitial keratitis	2	0
	356	948

Monocular Blindness.—The records of this condition were made for comparison and interest. The total number recorded is 948, and the males and females are about equal. It was also found that right and left eyes were equally affected. The sequence of frequency was cataract; leucoma, phthisis, and staphyloma; trauma; local infection; iridocyclitis; and glaucoma.

From this short report it will be appreciated that much remains to be done before comparison of figures and conditions can be made with those of more civilized countries.

I wish to thank the Director of Medical Services, Nigeria, for permission to publish this paper.

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A short article in *La Presse Médicale* of February 2 gives news about medicine in Germany to-day. In Western Germany there are 63,000 doctors as compared with 44,000 before the war. Medical students number more than 22,000 in the universities—in proportion to the population this is more than twice the number in the United States. Doctors are paid very little, and less than half the 17,000 in hospitals are receiving a living wage, so it is scarcely surprising that most of them have to take other jobs and are employed as night watchmen, musicians, and so on. This surfeit of doctors is due partly to the large numbers of refugee medical men and partly to the fact that during the war many hundreds of doctors were trained for service in the Forces. Those most affected are the young newly qualified doctors; the specialists are rather better off. Private patients are rare, and the doctors depend upon State payment for their treatment of insured patients; often they earn less than Post Office employees. There is virtually no freedom for the doctor in modern Germany, who is not even permitted to use his car unless the patient is more than two kilometres away from his home. He is not allowed to refuse to treat a patient. War and its aftermath have meant that Germans frequently fall ill, and the doctors, in spite of their great numbers, work twice as hard as they did before the war for about the same sum of money.

Reviews

HUMAN PHYSIOLOGY

Human Physiology. By Bernardo A. Houssay, M.D., Juan T. Lewis, M.D., Oscar Orías, M.D., Eduardo Braun-Menéndez, M.D., Enrique Hug, M.D., Virgilio G. Foglia, M.D., and Luis F. Leloir, M.D. (Translated by Juan T. Lewis and Olive T. Lewis.) (Pp. 1,118; 499 figures. £5 19s.) London: McGraw-Hill Book Co., Inc. 1951.

Professor Houssay and his colleagues are all professors or directors of physiology, pharmacology, or biochemistry in institutes of research in Argentina. No one section is officially written by any one author; the team takes collective responsibility for every page. The translation is excellent and the illustrations are well chosen, most being taken from the original papers quoted. There are ample and complete references to the original literature, both as footnotes to the pages on the matter under discussion and also at the ends of chapters to the main reviews and monographs.

This book is excellent in its approach to the subject. It is balanced, though it might be possible for a specialist to say that his aspect has not had justice done to it. It is to be compared with the standard textbooks of Starling and Halliburton in this country, and with Best and Taylor's in Canada, or Fulton-Howell's in the U.S.A. It has the great advantage of them all—that it is a first edition; it is new and therefore a comprehensive treatment of the application of physiology to the human subject in a framework and plan cast in the mould of physiology as it was in 1951; it is uninhibited by being written to a plan of earlier years and adapted as different aspects have grown or regressed in importance.

The personalities and authority of the authors are visible throughout, and the book is to be recommended to all physiologists, physicians, and libraries. Its sole disadvantage in England is its price.

A. ST. G. HUGGETT.

ADVANCES IN BACTERIOLOGY

Recent Advances in Bacteriology. Edited by J. H. Dible, M.B., F.R.C.P. Third edition by J. D. Maclennan, M.B.E., M.D., with the assistance of Mary Barber, M.D. (Pp. 325. 14 figures. £1 5s.) London: J. and A. Churchill. 1951.

Nearly twenty crowded years have elapsed since the last edition of this book, and the choice of subjects in rewriting it cannot have been easy. Staphylococcal toxins, the serological classification of streptococci, the typing of diphtheria bacilli, and the evolution of the sulphonamides are among those chosen, although much of the work on them was done in the 'thirties. The central feature of this edition is a group of six chapters on anaerobic infections. Three of these are devoted to tetanus and gas gangrene, and one to botulism: 27 pages may seem an excessive allowance for the last-named in view of its great rarity as a human disease, but it occurs also in animals and birds, and its toxin, as implied in these pages, has been intensively studied as a potential war weapon, defence against which would require universal immunization. Various forms of anaerobic coccal infections of wounds are also described. The authors accept Meleney's distinction between "post-operative bacterial synergistic gangrene" and "chronic undermining burrowing ulcer" and his statement that the streptococci concerned are respectively non-haemolytic and haemolytic. The final chapter in this group is on non-sporogenous anaerobic bacilli and particularly those Gram-negative organisms for which the generic term *Fusiformis* is so inappropriate and *Bacteroides* at least preferable. The author protests vigorously against the neglect of these common pathogens, and the frequent omission of methods of cultivation whereby their presence can be verified. The simple classification proposed is helpful, but it would not enable the bacteriologist to name all the strains he meets, and in fairness to him it should be said that to identify all such bacteria encountered in mouth and throat sepsis, pulmonary suppuration, bowel lesions and peritonitis, and uterine sepsis is simply impracticable until further study has provided better methods of isolation and stricter criteria of identity. Even so, the task of sorting out these mixtures of delicate and slow-growing organisms may often be too time-consuming for a busy clinical laboratory: this is the real reason for their neglect.

All the illustrations but one are in the chapter on morphology, which tells of additions to knowledge of the structure of the bacterial cell afforded by the electron microscope and by Feulgen staining. There are also two introductory chapters on bacterial physiology, one on the classification of colon and paracolon bacilli and *Shigellas*, and three on chemotherapy. The treatment of this subject is general, including history, commercial production, pharmacology, and clinical effects, whereas perhaps a greater attention to such aspects as species sensitivity and the mode of action of antibiotics on bacteria would be more appropriate here. Viruses are excluded as now entitled to books of their own. It would be easy to suggest other (bacterial) subjects which might have been included had space permitted. Many readers will prefer the exhaustive treatment of a limited number which has been adopted. The authors were faced with a heavy task in trying to present so vast an amount of accumulated knowledge, and have earned our gratitude by discharging it so thoroughly. Most chapters are fully documented, and the number of references independently checked in preparing the text is mentioned as having been 17,000.

L. P. GARROD.

INDIVIDUAL PSYCHOLOGY

Inferiority Feelings in the Individual and the Group. By Oliver Brachfeld. (Pp. 302. £1 5s.) London: Routledge and Kegan Paul. 1951.

The view is widely held among psychiatrists that the idea of the sense of inferiority and of the psychological means by which it can be compensated is too superficial a principle upon which to found a comprehensive system of psychopathology. None the less, the school founded by Alfred Adler has always had a strong appeal for historians, anthropologists, and thoughtful physicians, who have been able to see its application in many forms in their daily work. The Adlerian schema is perhaps a little too obvious and lacking in mysticism and emotionality to become really fashionable. Its acceptance in the English-speaking world has also been hampered by poor translation of the basic literature. This situation has recently been much improved by the teaching of Rudolf Dreikurs and his school in Chicago and by the recent publication of Lewis Way's *Adler's Place in Psychology*.* To these may now be added the book under review. It may be described as a comprehensive and scholarly compilation in which the author traces the origin of the "Gulliver complex" in philosophy and literature.

The author describes the present trend of the Adlerian school and its application to new fields of social psychology. The principle of compensation is followed from Montaigne, through Hobbes, to Pierre Janet, to whom the author gives full credit as the herald of modern psychopathology. The Adlerian system is lucidly presented, and there is a review of the literature in which it has been elaborated and extended. The author's own interest is clearly in the social applications of the theory, and at intervals he suspends the task of presenting the work of others to express his views on the relation of the sense of insecurity to recent political upheaval. In these chapters the reader may feel that Dr. Brachfeld is not giving him a chance to think for himself. The book is, however, an up-to-date and

*London: George Allen and Unwin. 1950. Reviewed in *British Medical Journal*, January 13, 1951, p. 76.

most valuable contribution to the literature of individual psychology, and it will be indispensable to those seriously interested in the subject. The translator, Marjorie Gabain, is deserving of high praise, and the impression is that little of the original has been lost.

ALEXANDER KENNEDY.

DIAGNOSTIC RADIOLOGY

Lehrbuch der Röntgendiagnostik. By H. R. Schinz, W. E. Baensch, E. Friedl, E. Uehlinger, and others. Fifth edition. Part 4: Skelett. (Pp. 514; 674 figures. M. 84.) Stuttgart: Georg Thieme. 1951.

More use is being made of radiography in diagnosis every year, and the appearance of a comprehensive treatise is therefore of the first importance. This volume is a worthy companion for Germany to the great British textbook which has just been completed, and which we recently reviewed. Naturally they follow very similar lines, but in some respects they are complementary, and the German work has several features which deserve attention.

The present volume is mainly on the spine, the skull, and the vascular system. Abnormalities of the vertebrae and their effect on the spinal column are fully described and illustrated. Outline sketches and drawings of sectional specimens make clear the changes which have occurred and their underlying pathology. The results of injury and disease are fully illustrated, and so clearly that they are readily appreciated without reference to the text. In an important section on myelography prolapsed disks and spinal tumours are discussed. The use of contrast media and of gases by injection is fully and exactly described and illustrated.

The article on the skull occupies 240 pages. Injuries and tumours of the skull are fully described, but the sections on ventriculography by Lindgren, and arteriography by Krayenbühl, are of quite exceptional interest. They are illustrated by superb radiographs with clear explanatory diagrams, and they include precise details of the exact technique required in these difficult and important fields. The application of these methods and the diagnosis of cerebral tumours is fully elaborated and finely illustrated, and represents a technical achievement of a very high order.

Radiography of the temporal bones is discussed in a very original and suggestive article. The localization of foreign bodies in the eye is dealt with in a fascinating study in which most ingenious methods are described. In a brilliant chapter on angiography Lindbom describes methods as daring as they are successful and produces illustrations of the results obtained which are really amazing.

In a short review it is impossible to do justice to the vast amount of valuable and original material contained in this volume. It concludes with an ingenious series of outline sketches covering the whole field of differential diagnosis throughout the skeletal system and serving as a visual index to the whole volume. The sketches will be valuable to the teacher and a help to those who do not read German. But such a book as this is worthy of the most careful study and, indeed, will fully reward the effort to be able to read the great language in which it speaks.

HENRY SOUTTAR.

GLAUCOMA

The Glaucomas. By H. S. Sugar, M.D., F.A.C.S. (Pp. 469; 123 figures. £4 4s.) London: Henry Kimpton. 1951.

This small book on glaucoma is a useful and interesting summary of modern views on this perplexing disease. The cognate questions of the physiology of the production, circulation, and drainage of the intraocular fluids and of the maintenance and variation of the intraocular pressure are briefly discussed before the more clinical aspects of the subject—the primary and secondary glaucomas, their aetiology, diagnosis, and treatment by medical and surgical methods.

The amount of recent research directed towards solving the problems of the intraocular pressure and its pathological variations has been enormous, with the result that our views on this subject have changed considerably over the last ten years. The reader will find an adequate presentation of these problems in this book, and, although some will question certain of the conclusions, the general teaching is sound. The author accepts, for example, Friedenwald's unconfirmed claim that Schlemm's canal has an afferent arterial supply and that consequently primary glaucoma is caused by a diminution of the plasma content of this canal owing to sclerosis of these vessels; this results in a failure in osmotic attraction into the canal which would facilitate drainage if it existed. Many authorities would question these assumptions. But on the whole a difficult subject is treated in considerable detail with great fairness and common sense, and new additions to our knowledge of the theoretical problems involved, as well as the immense amount of new techniques in treatment, both with regard to recently introduced miotics and surgical procedures of recent development, are adequately assessed. There is an effective and challenging final chapter on the presentation of popular educational programmes and the conduct of glaucoma clinics to deal with the sociological and administrative problems offered by this disease.

STEWART DUKE-ELDER.

A DOCTOR'S ADVICE

The Doctor. His Career. His Business. His Human Relations. By Stanley R. Truman, M.D. (Pp. 152. £1 4s.) London: Baillière, Tindall and Cox. 1951.

In introducing this book I cannot do better than quote the last paragraph of Dr. Truman's introduction: "The purpose of this book is to interpret for the medical student, resident and practising physician, the professional problems as well as the relationships and responsibilities of the physician to the patient, the public, and his fellow physicians, so they may develop an understanding and a feeling of what is meant by the practice of medicine." The book faithfully carries out this intention. It contains the ripe experience of a doctor trying to convey just the advice he so badly needed when he graduated, and which he failed to get.

He begins by discussing the reasons why students choose medicine as a career, and goes on to the various branches open to the new graduate. As a general practitioner he strongly presses the claims of family practice, but much of what he says applies to any branch of medicine. He discusses the prospects in the various specialties, the pros and cons of town and country, of independent *versus* group practice, and all his opinions are backed up by what he has seen in investigating many kinds of practice in various States. In view of the discussion over here of a possible College of General Practice it is interesting to note that Dr. Truman strongly advises all general practitioners to aspire to membership of the American Academy of General Practice, whose object is "to refocus the attention of the public and the profession on the importance of the general practitioner." One of its requirements from its members is 150 hours of postgraduate education every three years. The Academy is now, next to the American Medical Association, the largest medical organization in the U.S.A.

Shrewdness characterizes every chapter, not least that on equipment of the doctor's "office." Dr. Truman thinks that a general practitioner really established should have a secretary-receptionist, a nurse-assistant, and a laboratory-technician-assistant. It will be evident that the book is primarily addressed to the U.S.A. doctor, but *mutatis mutandis* it would interest any doctor anywhere, especially if he is young. No aspect of practice is left untouched, and the advice obviously comes from one who knows what he is writing about and does it in a most agreeable way. I congratulate the author on striking an original line in a neglected field and feel sure his book will be a success.

A. COX.

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MEDICAL TREATMENT OF HYPERTENSION

Over the last 100 years the life expectancy of the population has been doubled, so that now the *average* life-span is close to three-score years and ten. This is largely attributable to the decline in infant mortality, improved nutrition, the greater safety of childbirth, the spectacular achievements of surgery, and the successful war against parasites and microbes. Such victories have thrown into relief our failure to deal effectively with rheumatic fever, cancer, atherosclerosis, and essential hypertension, and emphasize the fact that real cures are unlikely to be found until the aetiology of a disease is properly understood. Of the four mortal diseases just mentioned essential hypertension is the most prevalent. According to Master and his colleagues[1] it occurs in 5% of young adults, 30 to 40% of those over 40 years of age, and in 65 to 75% of all persons over 70 (the lower figures apply to men, the higher to women). It is responsible for 15 to 20% of all deaths in people over 50.[2 3] Of these deaths about 60% are cardiac, 20% cerebral, and 10% renal.

It is impossible to assess the value of any treatment unless the natural history of the disease is known. Fortunately there have been several excellent long-term studies of untreated patients, such as those by Janeway,[4] Blackford, Bowers, and Baker,[5] Keith, Wagener, and Barker,[6] and Bechgaard.[7] From these and similar reports certain important facts emerge. First, the mortality rate in men is at least one and a half times that in women except in malignant hypertension, when it is equal. The two sexes should therefore be considered separately. Secondly, the prognosis in any series depends greatly on the nature of the material, and survival rates can be compared only when the patients are grouped according to certain well-defined criteria. In simple terms these are based on the general level of the blood pressure itself and on the reactive behaviour of the ocular fundi, the heart, and the kidneys—four grades of severity being usually recognized. In this kind of grouping not enough attention has been paid to occlusive coronary atherosclerosis as a complicating factor which may alter the whole course of the disease. Thirdly, the fatality rate is about 10% in five years and 20% in ten years for patients in group 1, 20% and 40% respectively for group 2, 40% and 80% for group 3, and 95 to 100% for group 4, being higher for men and lower for women in the first three groups. Lastly, in the unselected series of cases of essential hypertension the death rate is about twice that in the general population.

There is now little doubt that surgical treatment has materially lowered the fatality rate of hypertension.[8] The question at issue is whether modern medical treatment can do better. The subject was recently discussed at a meeting of the Section of Medicine of the Royal Society of Medicine (reported on page 597 of this issue). Conservative treatment in the past has meant little beyond increased rest and relaxation, avoidance of mental and physical stress, weight reduction, and sedatives. With this kind of regime and the moral support of a doctor about 60% of hypertensive patients remain more or less free from symptoms. It is common knowledge that headaches, fatigue, insomnia, and dizziness occurring in patients with high blood pressure are often due to an associated anxiety state, and psychiatric help (accidental or by design) may be of great benefit. Much of the earlier criticism of surgical therapy was based on the belief that the drama associated with the operation might well remove symptoms by the influence of suggestion. Physicians must apply the same strict criteria to their own results that they advised surgeons to apply. This means long-term studies of the fatality rate in treated and untreated patients, as well as objective evidence concerning the ocular fundi, the heart, and the general level of the blood pressure.

Kempner[9] has reported that 70% of 777 patients treated by the rice diet showed objective improvement: for example, the T wave in lead I became upright in 122 out of 224 cases in which it was previously inverted. This is impressive, and Kempner's good results have been achieved by others. The essential feature of the diet is its low sodium content, which must not exceed 0.5 g. daily.[10] It is a mistake to assume that such a diet can be given only in hospital; on the contrary, a good housewife, feeling

1 *J. Amer. med. Ass.*, 1943, **121**, 1251.
2 Bell, E. T., and Clawson, B. J., *Arch. Path.*, 1928, **5**, 939.
3 Fahr, G., *Amer. J. med. Sci.*, 1928, **175**, 453.
4 *Arch. Int. Med.*, 1913, **12**, 755.
5 *J. Amer. med. Ass.*, 1930, **94**, 328.
6 *Amer. J. med. Sci.*, 1939, **197**, 332.
7 *Acta med. scand*, 1946, Suppl. 172.
8 *Hypertension*, edited by E. T. Bell, 1951, London, p. 429.
9 *Ann. Int. Med.*, 1949, **31**, 821.
10 Corcoran, A. C., Taylor, R. D., and Page, I. H., *Circulation*, 1951, **3**, 1.
11 Dock, W., and Frank, N. R., *Amer. Heart J.*, 1950, **40**, 638.
12 *British Medical Journal*, 1951, **1**, 1217.
13 Kauntze, R., and Trounce, J., *Lancet*, 1951, **1**, 549; **2**, 1002.

responsible for her husband's health, is often more certain of maintaining a strict diet than many hospital kitchens. The cation-exchange resins[11] may be expected to play an increasing part in the control of hypertension by dietetic means.

Hexamethonium bromide has passed through its early trials with greater success than was at first predicted. The largest series so far reported is that by Smirk and Alstad,[12] who describe their results in 53 cases, but only 32 of them had been treated for six months or more. Both Smirk and Rosenheim, who spoke at the R.S.M. meeting, prefer parenteral therapy, but oral administration should not be despised. Hexamethonium tartrate may be used when large doses are necessary, so that there need be no risk of bromism. Smirk has emphasized the value of combining hexamethonium with a low sodium diet. This has much to recommend it. For patients on this diet the dose of oral hexamethonium usually lies between 250 and 750 mg. three times daily, and serious variations in the day-to-day response can be countered by altering the diet rather than by juggling with the dose of hexamethonium. There is little evidence to favour the often expressed view that hexamethonium soon loses its effects, that it is of little value for prolonged treatment. On the contrary, there is every reason to believe that the building-up of tolerance is short lived and that the final maintenance dose is known within two or three months, after which it does not have to be increased, although occasionally it may have to be lowered. Side-effects have proved less troublesome than expected and are usually easily countered.

Compared with the low sodium diet and hexamethonium, other drugs for lowering the blood pressure have proved unsatisfactory. This applies to thiocyanate, which is more difficult to handle, too toxic, and less effective; to "veriloid" (discussed by Dr. R. Kauntze at the R.S.M. meeting and in earlier papers[13]), which too often causes vomiting; and to various adrenergic blocking agents such as dibenamine.

The medical treatment of hypertension is likely to remain far from satisfactory until the cause of the disease is known. In the meantime a combination of a low sodium diet and hexamethonium may give the best results; but only a follow-up study over 5–10 years can show whether this treatment is superior to sympathectomy. Owing to the imperfections and troublesome side-effects of nearly all effective treatments and to the benign course of relatively mild hypertension, patients in groups 1 and 2 are probably best left alone, treatment being reserved for those in groups 3 and 4.

CORTISONE AND HYDROCORTISONE

Early publicity, despite the very careful wording of the original reports, quite understandably threw a spotlight on the dramatic rapidity of the relief which cortisone brought to those suffering from the painful and crippling effects of severe rheumatoid arthritis. It is only recently that critical assessments of the potentialities of this extremely important and powerful therapeutic weapon have appeared, and they deserve close study. About six months ago in this *Journal* Dr. E. W. Boland,[1] of Los Angeles, discussed three most important questions about cortisone therapy: Can suppression of rheumatoid arthritis by cortisone be maintained? Will continued administration lead to side-effects necessitating discontinuation? And will continued therapy cause irreparable damage to other organs, especially the adrenals? Enough patients have now been treated over periods of three months to one year or more to give at least partial answers to these questions. The first two are closely related, since the possibility existed that suppression of symptoms could not be obtained without side-effects so serious that reduction below the therapeutic dose would become necessary. Experience has in fact shown that the incidence of side-effects varies with the size of the maintenance dose. Physicians at the Mayo Clinic were able to maintain satisfactory suppression on doses of 75 mg. of cortisone a day or more in 29% of their patients and on smaller doses in the remainder.[2] Of the patients receiving the larger doses 63% showed side-effects, while only 21% did so on the smaller doses. Men were less prone to these side-effects than women, for in the smaller range of doses they appeared in only 5% of men but in 24% of premenopausal women and 31% of post-menopausal women. With the larger doses the comparable figures were much higher—50%, 72%, and 85%.

In an important report[3] published in the *Journal* three weeks ago a team of workers prominent in this country suggest that the significance of these side-effects should not be exaggerated. Facial rounding and irregularity of the menstrual cycle, they point out, are not serious enough in themselves to warrant cessation of treatment. Although the Mayo Clinic figures are high, most of the side-effects are reversible and did not, in fact, lead to discontinuation of the treatment. While, therefore, a careful watch should be

[1] *British Medical Journal*, 1951, **2**, 191.
[2] Ward, E. W., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S., *Proc. Mayo Clin.*, 1951, **26**, 361.
[3] Copeman, W. S. C., Savage, O., Bishop, P. M. F., Dodds, E. C., Kellie, A. E., Stewart, J. W., Glyn, J. H. H., Henly, A. A., and Tweed, J. M., *British Medical Journal*, 1952, **1**, 397.
[4] *J. Amer. med. Ass.*, 1951, **147**, 1538.
[5] *British Medical Journal*, 1952, **1**, 341.

kept for more serious side-effects such as the masking of an intercurrent infection, activation of a quiescent tuberculous lesion, or diabetes, the appearance of minor complications of treatment should not lead to precipitate withdrawal but only to a greater watchfulness. By carefully selecting their cases Copeman and his colleagues[3] were able, within a period of treatment of only three months, to get 17 out of 20 patients back to work on maintenance doses of cortisone without the appearance of serious side-effects.

No one has yet put forward evidence to substantiate fears of permanent adrenal suppression. Freyberg and his co-workers[4] found that in just under half of their 24 patients treated continuously for at least 100 days the Thorn test showed that adrenal function had been suppressed after withdrawal of cortisone, but this did not prove to be of clinical importance, and in every case recovery occurred within six weeks. The relapse rate after discontinuation is high: in Freyberg's cases 83% relapsed, nearly all within a month, to the condition they were in before treatment began. Since the action of cortisone is purely suppressive, this is to be expected, and it emphasizes that for cortisone treatment to be practical it must be prolonged, unless it is used for other special reasons. These include the treatment of a patient whose arthritis is rapidly progressive, when deformities due to spasm may be corrected during the time that cortisone brings relief. Similarly it may be useful when orthopaedic surgery or manipulation is indicated. But if it is to be used for prolonged treatment of a disease such as rheumatoid arthritis with a long natural history, measured often in years, it is clear that studies over still longer periods are much needed. In addition to relapse of the disease the appearance of a post-cortisone withdrawal syndrome, as recently described by Duthie,[5] is a serious complication. It occurred in 21% of Freyberg's patients. On withdrawal of cortisone not only does the disease relapse but sometimes in addition severe malaise with depression, fatigability, anorexia, and weakness, combined with the symptoms of relapse, may give rise to a distressing illness. Very gradual withdrawal of the hormone, when this is decided upon for any reason, is an essential precaution.

Since it seems probable that hydrocortisone (Kendall's compound F) is the naturally occurring active principle of the adrenal gland, studies of the effects of this substance may provide the solution to some of these problems of cortisone therapy, and in the opening pages of this issue Dr. Boland does suggest that hydrocortisone may be more effective and, possibly, that its enhanced antirheumatic action is not associated with an increased incidence of side-effects. The acetate ester of hydrocortisone is not so active as cortisone acetate, but the non-esterified product—hydrocortisone (free alcohol)—appeared to have approximately 50% greater activity than cortisone itself. While these differences may be accounted for in part by the difference in solubility, this may not be the whole answer, especially if the reduction in side-effects is confirmed.

Only very tentative conclusions may be drawn at present about the practicability of prolonged cortisone therapy. It seems clear that rheumatoid arthritis of itself is not an absolute indication for cortisone, and very careful selection of cases is required. But the criteria for selection have not yet been defined. It has not so far been shown that the very early, acutely active disease is the most suitable for long-term treatment, since the dose which may be needed in this type of case has not been established. It remains to be seen whether cortisone treatment maintained for years on end will produce better final results than other modern methods, or whether simultaneous treatment with, for instance, gold will reduce the relapse rate after withdrawal of cortisone. Cautious conclusions are still necessary, but it is certain that these detailed studies of rheumatoid arthritis, in which the disease processes are being carefully observed and, what is more important, being measured, will lead to the development of more effective control in the foreseeable future.

SHERRINGTON

In *A Mathematician's Apology* the late G. H. Hardy had some interesting things to say on age and intellectual activity. Poets and mathematicians, he thought, had often done all their original work before they were 40, an age at which novelists and biologists were only just coming to maturity. Certainly this seems to have been true of Sherrington, though he was clearly from the first a brilliant student. Chance took him to Cambridge rather than Edinburgh, and so to the then most stimulating centre of physiology—particularly of the nervous system—in Britain. Good fortune enabled him to travel in Spain, Italy, and Germany and to work with a number of the leading scientists of the period, an opportunity much rarer for the promising young man to-day than it was in the heyday of Victorian insecurity and freedom. Sherrington grew up at a time when clinical neurology, neurohistology, and the physiological study of both brain and peripheral nerve were all very actively and fruitfully pursued, and not least in England, by such men as Hughlings Jackson, Gowers, and Ferrier.

And it was thus that in 1891, when he was already 34, he was at last ready to start his life's work.

The historical circumstances were powerful, the opportunity of having so many experimental animals probably unique, and Sherrington had a mind that loved precision and order. It was his continual search for the exact word, the completely accurate statement, which made his lectures and his writings difficult and yet at the same time enabled him to see more deeply than his contemporaries and not to take anything for granted. Through his long training he had learned the scientist's supreme wisdom, which is to know how to ask the right questions, how to frame the experiment within the available technical resources so as to obtain an unequivocal and significant answer. The result was *The Integrative Action of the Nervous System.*

He reached his 60th birthday in the middle of the first world war, not long after his transfer to Oxford. Had he died then, or thought chiefly of his impending retirement as so many men might, there could hardly have been an Oxford school of neurophysiology to give so much to the world in training able men and analysing the mechanisms of the spinal reflexes. But he worked on for another 20 fruitful years, and in *Man on His Nature* celebrated his retirement with a scrupulous analysis of the nature of the mind, in which he came to the conclusion that it was something other and more than the integrated functioning of a myriad of nerve cells, a view which commanded great respect and agreement, though here and there dissident opinions and voices were heard.

So another great Victorian genius is gone from us. But his work will endure as long as civilization itself, and his example as a man of science who embraced the humanities will serve as a steadying influence to those who in the contemporary world are trying to challenge the materialism that too facile an interpretation of science encourages.

PROPHYLAXIS AND TREATMENT OF MALARIA

Among the most important of the findings of Fairley and his co-workers[1] which made possible the military successes in Burma and the Pacific in 1944–5 was that the large-scale introduction of treatment with mepacrine abolished blackwater fever. This was observed in both New Guinea and West Africa. In 1942 in New Guinea the use of quinine as a suppressive drug led to chronic latent or recrudescing falciparum malaria, in the presence of which blackwater fever was prone to develop. Later, with the same strain of *Plasmodium falciparum*, Fairley found that 10 gr. daily completely failed to suppress overt attacks or to produce radical cure in experimentally infected volunteers. For this reason alone the use of quinine as a suppressant and for treatment of chronic falciparum infections should be discontinued. Whether quinine is given by the intramuscular, intravenous, or oral route the danger of blackwater fever is present in patients with chronic falciparum infections who have previously taken this drug. It should not be forgotten, moreover, that in patients severely ill with cerebral malaria caused by *P. falciparum* blood slides may show only scanty parasites, and also that vivax parasites have been mistaken for those of *P. falciparum*. The latter error is particularly likely to occur when thick films are used and where pathological services are ill developed or during epidemics when the practitioner is swamped with work. A further pitfall is the case presenting as overt vivax, ovale, or quartan malaria, but also suffering from a latent chronic falciparum infection without falciparum parasites being present in the blood. The administration of quinine in such cases will cure the overt infection but may precipitate blackwater fever. For these reasons there is much to be said for the avoidance altogether of quinine and the use in its place of one of the synthetic antimalarial drugs.

For severely ill patients in whom speed of action is essential, mepacrine musonate given intramuscularly in doses of 0.36 g. is probably the drug of choice from among those at present available. It produces an effective concentration in the blood 15 minutes after injection and may be repeated in a few hours if necessary. Fairley[2] stated that chloroquine is probably the most potent schizonticide yet discovered, and elsewhere in this issue Drs. R. N. Chaudhuri, N. K. Chakravarty, and M. N. Rai Chaudhuri report favourably upon it. Scott[3] incorporated 400 mg. chloroquine (base) in 500 ml. sterile saline and administered the solution by intravenous drip over one hour. With this technique no serious toxic symptoms developed, and very rapid cures were obtained. Scott considers this to be the best method of treating patients severely ill with falciparum malaria. If, however, quinine is preferred in such cases an intravenous injection will ensure prompter action than one given intramuscularly, and if administered slowly few side-effects will occur. Intravenous quinine injected rapidly may produce a dangerous drop in blood pressure. Intramuscular injections, though followed by less prompt benefit than intravenous, incur the same risk of blackwater fever plus the possibility of sequelae such as abscesses and painful nodes. In falciparum malaria, therefore, they are best avoided.

In the treatment of the vivax attack and of falciparum infections when cerebral symptoms are absent, chloroquine given orally is probably the drug of choice, acting more rapidly than any other schizonticide. Mepacrine in suitable dosage is almost as effective, and experiences in the 1939–45 war showed it to be a schizonticide acting more rapidly than quinine when administered orally.

Camoquine is a new 4-aminoquinoline drug, and as reported by Chaudhuri and his colleagues appears to be second only to chloroquine in schizonticidal properties.

[1] *Trans. roy. Soc. trop. Med. Hyg.*, 1945, **38**, 311; ibid., 1946, **40**, 105, 229, 621.
[2] *British Medical Journal*, 1949, **2**, 825.
[3] *Amer. J. trop. Med.*, 1950, **30**, 503.
[4] *British Medical Journal*, 1950, **2**, 7.

It is regrettable that accurate assessment of the relapse rate after the various forms of treatment they used was impossible, as they were working in an area where malaria is endemic and fresh infections common.

Chemotherapeutic prophylaxis of malaria may be effected by drugs acting on the pre-erythrocytic cycles of the parasite or by schizonticidal suppressants. Among the former proguanil occupies pride of place and is the least toxic of all known antimalarials. Tissue forms of falciparum parasites have been shown[1] to be 30 times more sensitive to its action than blood forms, and their growth in the liver to be completely inhibited. The drug is rapidly absorbed and excreted so that daily dosage with 100 mg. is recommended for maximal effect. Although Chaudhuri and his colleagues have found the results of suppression with chloroquine to be better than those with proguanil it should be noted that in these trials the dosage of proguanil was lower than usually advised. It should also be remembered that proguanil given daily will bring about effects on the tissue phases of the malaria parasite unattainable with any other drug, and also that it effectively sterilizes gametocytes. When suppressants are taken without strict supervision malaria is encountered even among those using drugs known to be capable of suppressing the disease completely. In this connexion Bruce-Chwatt and Bruce-Chwatt[4] found the comparative incidence of malaria among non-Africans in Nigeria to be 10% in proguanil-takers, 21.5% in quinine-takers, 22.6% in mepacrine-takers, and 22.5% in chloroquine-takers.

It is known that proguanil when given in doses too small to be curative may induce resistance of the parasite. Such doses taken by indigenous Malayans may account for the occurrence there of resistant strains of malaria parasites as reported on page 564 by Drs. T. Wilson, D. S. Munro, and D. R. Richard. It is unfortunate that in their cases irregular dosage of suppressive proguanil cannot be excluded. Experience in the last war showed that suppressive discipline was bad in many units where it had been thought to be satisfactory. A lapse in administration of proguanil may permit growth of the tissue forms of the parasite—i.e., the forms which are most susceptible to proguanil.

Many problems concerning the chemotherapy of malaria remain to be solved, but we now have potent synthetic remedies of tried worth, capable of controlling the disease and of abolishing the risk of blackwater fever. It would seem rational to use them rather than older remedies with their associated dangers.

LEFT HAND, RIGHT HAND

It has long been known that the phenomenon of handedness is not peculiar to man. Consistent individual preferences in the use of one hand rather than the other have been reliably reported in rats, monkeys, and apes, although there is no evidence to suggest that a general tendency to right-handedness exists at any level below that of man. In a recent study of handedness in monkeys, Glees and Cole[5] describe consistent individual hand-preferences in the performance of a simple manipulative task, but find that the left hand is preferred in at least as many animals as is the right. This is in full accord with Yerkes's[6] classical observations on handedness in chimpanzees. In general, hand-preference in primates is consistent for a wide range of manual tasks, although the degree of dominance of one hand over the other varies to some extent in different animals.

The origin of individual differences in handedness is far from clear. Glees and Cole put forward the suggestion that they may be due, in part at least, to a virtually fortuitous asymmetry of neural organization. In studying pyramidal degeneration after lesions of the motor cortex in monkeys they were struck by the considerable variation in the number of fibres which remain uncrossed, and are led to suggest that "... in motor acts which demand greater skill, that hemisphere which gives rise to a comparatively large proportion of crossed fibres has a slight advantage over the other." Variability in the number of decussating sensory fibres which reach one hemisphere through the thalamus is also proposed as an additional cause of lateral dominance. Interesting as these suggestions are, it must be borne in mind that no direct evidence is adduced in support of either hypothesis. Until this is done, the explanation advanced by Glees and Cole must be regarded as wholly speculative.

In man it is generally held that dextrality is linked in some way with the evolution of language and its unilateral representation in the cortex. Indeed, the concept of cerebral dominance has largely arisen in connexion with aphasia and kindred disorders of speech. Recent studies, however, suggest that the relationship of handedness to aphasia may be more complex than has hitherto been supposed. In particular, the incidence of aphasia in left-handed individuals with unilateral cerebral lesions shows considerable variability. Thus Conrad,[7] in a survey of 800 cases of brain injury, reports on 18 cases in which dysphasia was associated with pre-existing left-handedness. In these cases the lesion was left-sided in ten and right-sided in only seven. Further, the language disorder in all these cases was considerably less severe and long-lasting than in comparable cases of dysphasia in right-handed individuals. Conrad is therefore led to suggest that in left-handed persons there is typically some degree of bilateral representation of speech and that the dominance of one or other hemisphere for this function is seldom as complete as in the right-handed. In his view, left-handedness expresses a less-advanced degree of specialization of cerebral function.

The view that handedness itself is less firmly developed in sinistrals finds some support from a recent inquiry into consistency of hand-usage among healthy adults. Humphrey,[8] on the basis of a questionary distributed among 70 left-handed and 35 right-handed male subjects, reports far greater consistency of hand-preferences in the latter group. Many self-styled "left-handers" are, he believes, more fittingly described as "ambilateral." If the weaker hand-dominance of the left-handed reflects less determinate cerebral dominance, the results of Conrad and others on the incidence of dysphasia among

[5] *Experientia*, 1951, **7**, 224.
[6] *Chimpanzees*, 1943, Yale University Press.
[7] *Nervenarzt*, 1949, **20**, 148.
[8] *Brit. J. Educ. Psychol.*, 1951, **21**, 214.

sinistrals find a measure of explanation. If cerebral dominance is less firmly established in relation to manual skill, it is not unreasonable to suppose that language will enjoy a similar freedom from rigid unilateral control. This, however, is a hypothesis which will require to be tested by large-scale clinical and statistical investigation. At present, all that can be said with certainty is that the relation of "handedness" to "brainedness" is by no means as clear-cut as has been supposed in the past.

NAILING THE FEMORAL NECK

The multiplicity of instruments originally designed to facilitate nailing the femoral neck remain as a monument to the anxiety with which the operation was originally approached. The elderly patient's further existence without a nail is so unhappy, and the strain of the well-conducted operation so small, that no patient, unless the victim of some urgent crisis such as bronchopneumonia or cardiac failure, should be denied the consolation of the operation. Mr. D. O. Williams and Mr. E. K. McLean, who report their technique in this issue, are not alone in having reduced the operation to its barest essentials, and many surgeons are content to dispense with the hinged gauge and rely on their sense of touch and the radiographic position alone. With the exception of the unavoidable complication of avascular necrosis of the femoral neck, "the bad results of nailing are the results of bad nailing," as Eric Lloyd has emphasized. The success achieved by Williams and McLean is therefore a tribute to their careful technique, though it would have been interesting to know their failures due to necrosis. Even this complication is losing its terrors with the introduction of the plastic femoral head. Other surgeons are not so happy to dispense with the cross-pin. In the aged the nail is almost entirely dependent on the strength of the cortical bone of the great trochanter for its fixation, and if this is thin or widely opened by the pin-starter its grip is very weak. Although the majority of extrusions are due to absorption of the neck or slipping of the pin, nature tends to extrude it even when it is doing its work successfully, and the insertion of a cross-screw, which adds little to the time of operation and is readily removed, has no disadvantages. The pin which is fixed to the nail tends to break if there is any alteration in the angle of the nail and is to be avoided.

With a simplified technique of operation there is room to simplify the post-operative regime, which in most hospitals still drags out a weary three months. Confidence in early weight-bearing, from the surgeon's point of view, is dependent on a good position of the nail, good impaction, and a relatively horizontal fracture line; and from the patient's point of view on the redevelopment of effective muscular control. The surgeon's requirements are apparent from the beginning, and the patient's progress is obvious at the end of the first month. There is no reason why the selected patient should not start weight-bearing at this time—in fact an appreciation of the importance of compression strain on bony union would encourage such attempts. Once such a regime is started it is probable that the period of bed rest would be further shortened and the more doubtful cases included in the early ambulatory group. Three months' bed rest is a severe test of the fitness of the elderly patient.

A short period of preliminary traction by either a tibial pin or skin traction is a great comfort to the patient, and tibial traction has the added advantage of almost always reducing the fracture, thus enabling the patient to be placed on the operating table without any forcible preliminaries. Such pre-operative treatment is a necessity in hospitals in which an emergency operation cannot be performed. It is true that a short period of waiting will occasionally allow a complication to develop and so prevent operation before the end of the first week. On the other hand, too rapid assessment of the case will probably result in some operative tragedies. Before the emergency operation can be endorsed, it remains for its proponents to prove that it lowers mortality, lessens complications, and produces results as good as those obtained by other methods.

CIBA FOUNDATION

The *Report* for 1951 shows an ever-increasing valuable activity of this charitable trust (which was founded by the well-known Swiss firm in 1947) for promoting international co-operation in medical and chemical research. A series of international colloquia have again been held at the Foundation's house in Portland Place, on such subjects as the visceral circulation, isotopes in biochemistry, and the control of anterior pituitary secretions. Many foreign medical men have been entertained, and particular attention is being given to the promotion of Anglo-French medical relations by the provision of scholarships for British clinical postgraduate students to visit France for short periods (see *Journal*, March 8, p. 555) and for French workers to come here, and by bringing together the editors of the *Lancet*, *British Medical Journal*, *Presse Médicale*, and *Semaine des Hôpitaux* to encourage co-operation and awareness of one another's activities and points of view. The Foundation has also collaborated with the British Council and the Foreign Office (German Section), and provides a home for the Hunterian Society's museum and library and for meetings of the Renal Association. Very close relations with the Royal Society of Medicine have developed, part of its library being temporarily stored in Portland Place, and Fellows of the R.S.M. being able to stay there when the rooms are not required for foreign visitors. The Foundation is building up its own library, chiefly of books and periodicals on endocrinology. Altogether it is coming to occupy a position of key importance in the organization and international relations of British scientific medicine, and the trustees—Dr. E. D. Adrian, O.M., Lord Horder, Lord Beveridge, and Mr. Raymond Needham, Q.C.—and the executive council under them, of which Dr. G. E. W. Wolstenholme is the secretary, are to be congratulated on this valuable achievement after only two and a half years of active work. There was clearly a need for the services the Ciba Foundation is now so imaginatively supplying, and it has a great part to play in future development.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

FOOD-POISONING

BY

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Food-poisoning is a difficult term to define, but through common usage it is accepted as meaning an acute intestinal disturbance coming on within a few hours of the consumption of unwholesome food or drink. It is distinguished from other food-borne infections such as enteric fever, dysentery, or primary abdominal tuberculosis by the occurrence of acute gastro-enteritis, though intermediate cases do occur in which the differential diagnosis, particularly from that of dysentery, may cause difficulty.

Food-poisoning may be due to injurious chemical substances, poisonous plants, or harmful bacteria or bacterial products in food. The most usual type of food-poisoning encountered in this country is bacterial in origin, being caused by organisms of the *Salmonella* group. The disease is due to the multiplication of these organisms in the intestinal tract of the host and is known as the "infective type." Food-poisoning due to the ingestion of bacterial products is also fairly common. Some bacteria while growing in food are able to produce toxic substances which on ingestion cause vomiting and diarrhoea; this disease is known as the "toxin type" of food-poisoning. In a report on food-poisoning in England and Wales during 1950, of 3,979 recorded incidents, 2,170 were of bacterial origin (2,021 salmonella infection), 2 chemical, and 1,807 of unknown causation.

Infective Type

The *Salmonella* group of organisms, which now comprises about 250 recognized species, has its natural reservoir in birds, mammals, and reptiles. The organisms multiply in the intestinal tract of man, causing swelling of the mucosa of the stomach and small intestine and the production of a slimy exudate. The mucosa may become ulcerated. In severe cases these lesions may extend to the large intestine, and there may be an accompanying septicaemia. It is believed that a large number of salmonellae must be ingested in order to give rise to clinical symptoms. The organisms are widely distributed in nature and may be transferred to food in a variety of ways: the food may come from an infected animal, or may be contaminated with infected faeces from mice, rats, pets, or other animals; flies may transfer infected material to food; or human carriers may infect food during handling. Carriers sometimes give a history of a recent attack of diarrhoea, but many have had no intestinal disturbance nor have they been contacts of known cases.

As in most instances many bacteria or large quantities of their products must be ingested to cause symptoms, the most dangerous foods are those which are good culture media and which remain at a warm temperature long enough for bacterial multiplication to take place. These conditions are provided by meat dishes, gravies, and soups, particularly if reheated some time after preparation, and also by foods such as custards prepared at low temperatures. Most tinned foods are autoclaved during processing and are sterile, but once opened they are as liable to contamination as other foods. Small tins of ham can be autoclaved, but large tins are pasteurized, as autoclaving results in loss of palatability and changes in appearance. As a result, pathogenic organisms may be present in tinned ham, particularly in the large tins, and therefore it is wise to keep the tin in the refrigerator to limit multiplication and not to store it for too long. Hens' eggs are rarely infected, but a number of cases of food-poisoning have been traced to the consumption of ducks' eggs. The latter should be placed in boiling water for at least 10 minutes before being eaten and should not be used in the preparation of lightly cooked foods.

A number of other organisms are believed to cause food-poisoning, though their mode of action is unknown. Foods heavily contaminated with faecal organisms such as *Bact. coli* and *Proteus* have caused disease though the organisms themselves have not been shown to be pathogenic or to produce toxins.

One particular type of food-poisoning, caused by the eating of meat dishes which have been cooked the previous day and allowed to cool down overnight, is seen especially in those eating canteen meals, and is apparently caused by the anaerobic organism *Clostridium welchii*.

Toxin Type

Food-poisoning due to bacterial toxins is most commonly caused by the toxin produced by *Staphylococcus pyogenes*. The toxin is formed in the food during the growth of this organism. It is not destroyed by ordinary cooking processes, so that an infected food which is recooked may still cause disease. The food is usually contaminated by a food-handler who may have a septic lesion on the hands or may transfer the organism from his nose or throat via his hands to the food. Food which has been stored before consumption is the most common source of this disease. Ice-cream, cheese, as well as "made-up" reheated foods, are usually the cause. Other organisms such as non-haemolytic streptococci are known to cause the toxin type of food-poisoning. Little need be said about botulism. This toxin type of food-poisoning is extremely rare in Great Britain, only four incidents ever having been recorded. The disease is caused by the toxin of *Clostridium botulinum*, which acts on the central nervous system, causing diplopia, ocular paresis, and sometimes aphasia accompanied by vomiting and constipation.

Chemical Poisons

Food-poisoning may also be due to injurious chemical substances in the food, though such cases are comparatively rare. There are, however, many instances on record in which food has been in containers which have been used for chemical poisons. Some drinks may be contaminated with antimony or zinc as the result of placing acid liquids—for example, lemonades—or acid stewing-fruits in cheap enamel or zinc vessels. The symptoms usually develop very soon after drinking the fluid.

Death Cap

Some foods are poisonous in themselves. Poisoning due to the "death cap" (*Amanita phalloides*), a fungus eaten in mistake for mushrooms, is well known. The mortality rate is high, and children are particularly susceptible. The incubation period is between 4 and 24 hours, when the patient complains of very acute abdominal pain, vomiting, and diarrhoea. The vomit and faeces may contain blood and mucus. In severe cases anuria may follow, and later jaundice and cyanosis.

Allergy

Diarrhoea and vomiting may occur in individuals who have idiosyncrasies to certain foods. These attacks rarely last more than 24 hours. There is an acute onset soon after the food is eaten. Abdominal pain may be severe, but there is no rigidity. Though this syndrome may occur at any age, it is more common in childhood. Sometimes there is a history of other allergic manifestations in the patient or his family. The diarrhoeal stool from these patients usually contains eosinophil cells. The symptoms are cured by the injection of 3 to 5 min. (0.18 to 0.3 ml.) of adrenaline (1:1,000).

Investigation of Suspected Cases

In all suspected cases of food-poisoning it is important that the patient and the suspected food should be investigated as soon as possible, as knowledge of the causal agent may determine the treatment of the patient and the control measures to stop the spread of the disease. The patient's faeces, collected preferably during the acute stage of the disease and before starting treatment, should be sent to a laboratory. Laboratories provide sterile screw-capped receptacles containing spoons with which a portion of faeces may be transferred to the receptacle. If faeces are not available a sterile throat swab should be passed into the rectum, and care taken to see that the swab shows faecal staining; no lubricant or antiseptic should be used. Such swabs, which are suitable for bacteriological purposes only, must be transported to the laboratory before they begin to dry. Vomit may also be sent to a laboratory, although it rarely assists the investigation. Organisms of the *Salmonella, Shigella,* and staphylococcal groups are usually readily isolated if no treatment has been started. Suspected food, if available, should always be sent to the laboratory, as the proof that a particular food has caused disease depends on the correlation of the findings in the patients with those in the food. The assessment of the role of any particular organism isolated from food, other than the accepted pathogens such as salmonellae, shigellae, and some types of staphylococci, is extremely difficult.

Clinical Picture

The diagnosis of food-poisoning when a number of persons are affected usually presents few difficulties, but the diagnosis of an individual case may be far from easy. It should be borne in mind that an accusation of food-poisoning is a common form of blackmail brought against expensive restaurants. In such cases the doctor should never give a certificate to say that the patient has suffered from food-poisoning without the fullest supporting bacteriological and epidemiological evidence.

The symptoms in any single outbreak vary considerably in severity: some patients complain of no more than a vague discomfort which is disclosed only on questioning, while others are severely ill. These latter range from those whose main symptoms are diarrhoea and vomiting to those in whom these symptoms may be overshadowed by a clinical picture more closely resembling that of enteric fever. The symptoms vary with the agent which has caused the food-poisoning, but only the more usual types encountered in this country are dealt with. The most common type is that due to the bacterial infection of food and drink.

The incubation periods of the different types of food-poisoning may give some indication of the cause. Chemical poisons are usually rapid in their effect, symptoms occurring with a sudden onset in about half an hour or less. The toxin type, being due to the absorption of preformed bacterial toxin, also has a short incubation period, though it is longer than that of chemical poisons. The incubation period of the toxin type is between 2 and 12 hours, and there is also a sudden onset. Food-poisoning caused by the multiplication of organisms in the intestine has a longer incubation period, usually between 12 and 48 hours. The onset of this type may be sudden, though a number of patients complain of feeling ill before the main symptoms occur.

*Incubation Period of Food-poisoning**

Chemical	Bacterial Toxin		Infectious
	Staphylococcus	*Cl. welchii* and Streptococci	
0–30 minutes	2 hours	12 hours	20 hours

In all types the patient usually complains of nausea, vomiting, and diarrhoea. Commonly there is also headache, abdominal cramps, sweats, shivering, and giddiness. At the height of the illness the patient may be severely prostrated. In the toxin type the disease is of sudden onset and may be very similar to sea-sickness: the more severely ill patient is in a state of collapse and unable to stand; he sweats, and does not care whether he lives or dies. These patients commonly have a subnormal temperature; it is rarely above 99° F. (37.2° C.). They recover rapidly, usually in 24 hours.

In the infective type the disease develops rather more slowly and is accompanied by a rise in temperature, commonly to 102° F. (38.9° C.). The abdominal pain is of a colicky nature, starting usually in the epigastrium but spreading over the whole of the abdomen. Though the abdomen is tender there is no rigidity. The disease usually lasts for about four days and the patient complains of lassitude for some days more. The severely ill patient may look drawn and show signs of dehydration. If death supervenes it is usually about the tenth day of the disease, but death is unusual except in the very young, the old, or those with some additional serious illness.

The vomit is watery; it may be bile-stained, but is only tinged with blood if vomiting is excessive. The stools are watery, usually with faecal colouring, and they are very offensive. Blood is not often present and the mucus tends to be slimy, whereas in dysentery pus and blood are usual. In salmonella infections some patients may show the rose spots and the clinical picture of enteric fever. Patients generally recover rapidly. A certain number of the infective type may be operated upon as cases of appendicitis. It is probable that in these the appendix is inflamed, but the symptoms usually subside as the patient recovers, without necrosis of the appendix.

Complications may occasionally be encountered with salmonella infections. Very rarely empyema, purulent arthritis, or osteitis occur. Meningitis may be found more particularly in young babies. Occasionally patients have a long febrile period sometimes of a septicaemic type. After an attack of food-poisoning some patients become prone to dyspepsia and intestinal upsets.

Differential Diagnosis

Correct diagnosis is important from the point of view both of treatment and of preventing fresh cases. In dysentery vomiting is seldom a major symptom and rarely lasts for long. In addition the stool is usually blood-stained and contains large numbers of pus cells. Intestinal obstruction, intussusception, or volvulus usually cause localizing signs in the abdomen which are absent in food-poisoning. In practice these conditions are rarely confused with food-poisoning

A disease which occurs in this country is extremely difficult to distinguish from food-poisoning of the types already described. This condition, which occurs more commonly in winter and spring, cannot be traced to any particular food. It may start by affecting a number of persons at the same time, and when institutional outbreaks occur

*From *Modern Trends in Gastro-enterology*, edited by F. Avery Jones. Butterworth and Co., London.

secondary cases are the rule, usually with an incubation period of three to five days. A good review of this disease has been given by Hargreaves,* who refers to it as "epidemic diarrhoea and vomiting," though its more usual name is "the winter vomiting disease." In America similar outbreaks have been studied, and as the result of various investigations it seems probable that a filterable agent, probably a virus, is excreted in the faeces. The onset of the disease is sudden and not uncommonly occurs at night. The main symptoms are vomiting and diarrhoea, but vertigo may be a prominent symptom. Some patients have complained of acute upper abdominal pain, and some tenderness is elicited on deep palpation over the liver area. The differential diagnosis between these patients and true cases of food-poisoning presents many difficulties.

Treatment

Rest in bed is essential in all definite cases of food-poisoning, as recovery is always more rapid and relapses less common if this is observed. The treatment should be symptomatic. If poisoning by chemicals or fungi is suspected the patient's stomach should be washed out with the specific antidote if the offending chemical is known, otherwise with normal saline. In the early stages of other types of food-poisoning patients who are vomiting should be given a glass of warm water containing one teaspoonful of sodium bicarbonate in order to get rid of excessive mucus. If as the result of vomiting and diarrhoea the patient becomes dehydrated intravenous glucose saline should be administered. Persistent diarrhoea may be treated with bismuth carbonate or subnitrate. Opium in any form should be used only if there is no doubt about the diagnosis.

A specific antiserum for poisoning due to *Amanita phalloides* is available.† This serum should be injected intramuscularly and given as early as possible in the disease. The dose for a child is about 20 ml.

There are no specific remedies for bacterial food-poisoning. Antibiotics have been tried, but they have not given good results in the ordinary disease in which diarrhoea and vomiting are the main symptoms. Rarely some cases caused by salmonella infection may have a long-continued fever suggestive of septicaemia. In such cases chloramphenicol should be tried, as some patients seem to improve clinically; the drug does not, however, appear to shorten the period during which the organisms are excreted in the faeces, nor does it have any effect on the carrier condition. The usual dose of chloramphenicol for adults is 50 mg. per kg. of body weight in 24 hours. It is given at intervals of six hours, and should be continued until symptoms have been controlled, after which the dose should be halved for a further three to four days before stopping treatment. During the convalescent period the change to normal diet should be made gradually, particularly in patients who show a tendency to relapse.

Prevention of Spread

In salmonella food-poisoning the patient's excreta should be treated as in typhoid by the addition of 1:20 carbolic acid, corrosive sublimate, or other disinfectants which are known to act on Gram-negative organisms. The patient should be warned of the possibility that the organisms may be excreted for some time after recovery and told to wash his hands after defaecation and before taking food. He should not be allowed to handle food until laboratory tests have shown that the organism is no longer being excreted.

The prevention of bacterial food-poisoning depends on the education of the public in personal hygiene, in clean methods of food storage, and in clean methods of food preparation. Emphasis should be placed on the desirability of keeping food cool, preferably in a refrigerator, until it is ready for cooking; if it is not eaten immediately after cooking it should be rapidly cooled down and kept cool until it is reheated.

Under Section 17 (1) of the Food and Drugs Act, 1938, it is compulsory for a registered medical practitioner who becomes aware of or who suspects that a patient whom he is attending is suffering from food-poisoning to notify immediately the medical officer of health of the district, giving particulars of the case. If this is done early, laboratory investigations may determine the cause of the disease, the food at fault, and the source of the contamination. Such information will help to stop the spread of the disease.

British Medical Journal, 1947, **1**, 720.

†From the Central Public Health Laboratory, Colindale Avenue, London, N.W.9 (*Telephone:* Colindale 6041).

Next Refresher Course Article.—"Tenosynovitis and Tendovaginitis," by Mr. D. Lloyd Griffiths.

MEMORANDUM ON FAMILY PLANNING, WITH PARTICULAR REFERENCE TO CONTRACEPTION*

The subject of family planning is clearly of fundamental importance to the welfare of the community. The Royal Commission on Population, after sifting evidence from many sources, expressed itself as in no doubt of the need for a positive family-planning policy. The National Health Service Act makes provision for the care of pregnant and parturient women but does not lay down any plan of action in respect of family planning, though it may be argued that this should come under the heading of general medical services.

Family planning can be considered under three main headings: (1) the need for facilities for contraception; (2) marriage guidance; and (3) the treatment of involuntary sterility. As regards marriage guidance and the treatment of infertility, there is general and indeed increasing support from all sections of the community, irrespective of religious beliefs. But on contraception opinion is still sharply divided, and a certain number of persons, including all Roman Catholics, regard the use of appliances and withdrawal as morally unjustifiable in any circumstances. They object to public moneys being spent on any clinics where contraceptive teaching is given, or on contraceptive appliances. The use of the "safe period" is, however, accepted by the Roman Catholic Church, and, where spacing is indicated for health or social reasons for such patients, this method may be advised.

Inquiry into the Position

Towards the end of 1949 the Family Planning Committee of the Medical Women's Federation instituted inquiries to ascertain the position of family planning in respect of its three aspects—contraception, marriage guidance, and the treatment of involuntary sterility—as it stood after more than one year's working of the National Health Service Act.

The medical officers of health of 197 local authorities were circularized and were asked the following questions:

*A memorandum prepared by the Family Planning Committee of the Medical Women's Federation: Miss Beatrice Turner, F.R.C.S., F.R.C.O.G. (chairman), Dr. Annis Gillie, Dr. Olive Gimson, Dr. Margaret Hadley Jackson, Dr. Isabelle Little, Dr. Mary Macaulay, Dr. Joan H. Buchanan (honorary secretary), with Dr. Doris M. Odlum and Miss Josephine Barnes, D.M., F.R.C.S., as *ex-officio* members.

Information Received from 159 Medical Officers of Health of Counties and Cities in Great Britain

	No. of Replies Recd.	Negative	Affirmative	Affirmative Replies		Local Authority Own Clinics	Local A. plus Vol. Clinics	Voluntary Clinics Only	Remarks
				Contraceptive Advice Only	Contraceptive plus Subfertility and Marital Difficulties				
England	107	51	56	29	24	20	9	25	6 among negative replies (as classified) state suitable cases referred to antenatal clinics and some to gynaecological department at hospital. Four to voluntary associations such as Marriage Guidance Council and Family Planning Association
Scotland	39	29	10	3	5	3		3	5 in the 29 negative classification state antenatal clinics sometimes used. One stated clinics at considerable *distance* deliberately chosen if consultation advisable
Wales ..	13	8	5	3	2	2	1	2	4 out of the 8 negative replies state existing antenatal clinics meet need. Occasionally gynaecological department at hospital used

N.B.—Where totals do not tally it is because some replies were in the affirmative but no details were given of the type of advice or clinics available. Some replies stated, "No family planning arrangements," but proceeded to state, "Birth control clinic run by local authority." Such replies have been included in the affirmatives.

Do facilities exist in your area for the giving of advice on family planning? If so, are they for contraceptive advice only, or do they also cover the investigation of infertile marriage and of marital difficulties? Do you provide your own clinics, or do you rely on voluntary clinics in part or altogether?

In response to this inquiry 159 replies were received, and the answers are summarized in the Table. The most striking fact that emerges is that in well over 50% of all areas no clinics or special hospital out-patient facilities were available.

The deans of 27 medical schools were also circularized and were asked whether instruction on contraceptive technique and on the investigation and treatment of infertile marriage was given to medical students. Twenty-four replies were received, and these indicated that in most medical schools some sort of instruction, though sometimes an outline only, is included in the course of ordinary obstetric and gynaecological teaching. In only four were special lectures given on family planning and contraception. Practical experience in the fitting of caps was provided in a few cases by attendance at neighbouring voluntary or municipal birth-control clinics. Only two teaching hospitals held special sessions for out-patients where contraceptive advice was given, but a number held fertility clinics. Attendance by students at these was on a voluntary basis and was not regarded as an essential part of the curriculum. In fact, three medical schools expressed the opinion that these subjects were more satisfactorily dealt with after qualification.

Two main facts therefore emerge from this inquiry. First, that the facilities for family planning which existed in 1949—and there is little reason to suppose that there has been any great improvement since then—are totally inadequate for the needs of the community. This applies especially to contraception, since advice and treatment for infertility are given in many gynaecological departments which do not provide separate clinics for such cases. Secondly, the majority of medical students are qualifying without receiving an adequate introduction to all the aspects of family planning and cannot therefore be expected to give authoritative advice to their patients or to recognize the need for postgraduate training in the subject.

As to contraception, it is important that all general practitioners (apart, of course, from those who have religious or other objections) should have, as a minimum, knowledge of the best and safest methods. The public still turns naturally to the medical profession for advice on this matter: if this advice is not forthcoming, then those less reputable firms who advertise widely will replace informed medical advice. The methods advocated by such firms are often unsatisfactory and the accompanying literature distressing and distasteful. This has important repercussions, since failure of contraception is a serious factor in leading women to criminal abortion, and in addition family instability is increased when attempts made to space pregnancies fail.

The G.P. and Family Planning

The place of the general practitioner in the sphere of family planning is an obvious one, although no special provision is included in the National Health Service. Certain points may be made. It is manifestly impossible to prohibit any duly registered medical practitioner from practising any branch of the art or science of medicine. It is obvious, too, that over large areas of this country the family doctor is the only accessible person to give advice on contraception. It is not always so clearly recognized that the time required to fit an inexperienced or worried woman with a contraceptive appliance may be considerable and is not easily given when the case is seen during a surgery hour. The actual technique of fitting is relatively quick when accuracy is maintained by practice, except in a minority of cases. The training of the woman, however, to use the appliance and to ensure that she has accepted the idea of its regular use without reluctance or distaste often requires considerable time and patience. The general practitioner's knowledge of the woman herself and of her home conditions is an advantage often overlooked, especially when advice on marital difficulties is sought at the same time.

Many general practitioners undertake to give contraceptive information: most of these have made a special study of the subject, and some have had experience as medical officers at birth-control clinics. On the other hand, others prefer to send their patients to clinics which specialize in this particular branch of medical work. There are some patients, too, who prefer to consult a stranger on the question of contraception rather than turn to their own doctor. The outlay of considerable time on such work as part of the general medical services must necessarily deter some practitioners, especially those with the larger lists of patients.

Women seeking contraceptive advice fall into two main groups. First, those who on medical grounds have been advised to avoid pregnancy. It needs emphasizing that the general practitioner in such a case must ensure that his patient does secure contraceptive training from the best available source. Only too often the advice to prevent pregnancy is not accompanied by specific training on contraception or a letter to obtain such training from a clinic, hospital, or colleague. The second and continually expanding group is made up of women who wish to plan their family with intervals between the births of their children. It is these who present a challenge to the medical profession, since they can easily obtain non-medical advice which is increasingly freely advertised and is often of poor quality. Women who seek contraceptive advice

on these social grounds are glad to avoid the hospital out-patient department, and prefer either the local health authority or voluntary clinic, or their general practitioner. The advantage to the community resulting from the employment of general practitioners on a part-time basis at local health authority clinics for family planning is obvious.

With regard to infertile marriages the position is very different. Modern investigation and treatment of infertility is a complicated procedure involving elaborate pathological investigations and specialized treatment. Most general practitioners, in consequence, refer their patients to clinics or to hospital out-patient departments after a preliminary survey.

Concerning the supply of contraceptive appliances, the opinion was unanimous, after careful consideration, that these should not be prescribed on the N.H.S. form E.C.10. Abuse of the supply on extravagant lines would follow easily. The free source of appliances might lead to lack of attention to fitting, and thus to a high failure rate, particularly in large urban practices where experience in technique, time, and chaperonage may all be in short supply. Necessitous cases have always received consideration at voluntary clinics, and the case that is urgent both on medical and on economic grounds can be supplied from the hospital out-patient department.

Payment

The question of payment for giving contraceptive advice naturally arises. It would seem reasonable that in areas where there is no local authority clinic a suitably qualified general practitioner should undertake this work and should be paid by the local authority. It is questionable whether the giving of contraceptive advice on purely social grounds, in the absence of any medical necessity, may be considered as coming under the heading of general medical services. It is suggested, therefore, that general practitioners who are prepared to undertake this kind of work should be entitled to collect a fee from the patient even though she may be on their list.

It is fully appreciated that there are large areas of the country (especially in urban districts) where women have no difficulty in obtaining the contraceptive advice they seek. There remain very many who find this difficult or impossible to obtain in the absence of accessible clinics or of a family doctor who has both experience and time to give to the matter.

Summary

The following recommendations are submitted as being passed by the council of the Medical Women's Federation:

1. The provision of facilities for family planning must be regarded as an integral part of the National Health Service. All local health authorities should be *required* to provide clinics for family planning, and these should be run jointly by the local health authority and the regional hospital board in view of the extensive investigation and treatment required for subfertility.

2. It is recommended that when use is made of existing voluntary clinics *adequate financial support* should be given.

3. Contraceptive appliances should not be included in the schedule of goods to be prescribed on form E.C.10 in any future scheme.

4. We recommend that advice on family planning should be available to women who require it on medical grounds, and also *to women who ask for it for the purpose of family spacing*. Such advice should be given by (*a*) local health authority clinics; (*b*) voluntary family planning clinics staffed by doctors; (*c*) gynaecologists in hospitals; and (*d*) general practitioners with special training and experience in this work who are willing to allot the time to it. These should be specially selected, and a panel of their names should be available locally. A fee for this service should be paid by the local health authority or, alternatively, by the patient.

Reports of Societies

TREATMENT OF HYPERTENSION

A meeting of the Section of Medicine of the Royal Society of Medicine was held at 1, Wimpole Street, on February 26, when medical treatment of hypertension was discussed.

Professor M. L. ROSENHEIM recalled that a similar meeting five years ago, on the therapy of hypertension, had been chiefly devoted to surgical treatment. He then reviewed the medical methods that have been developed in recent years.

There was no evidence that the prognosis of mild, symptom-free hypertension was improved by any form of therapy, and reassurance with mild sedation should continue to be employed. Continuous treatment was indicated in the more severe forms of essential and renal hypertension, in both the benign and malignant phases. Such treatment could be tolerated only by those in whom the symptomatic relief was sufficient to outweigh the discomforts and inconveniences of therapy. Cessation of treatment was invariably followed by a recurrence of hypertension and of symptoms.

Salt Restriction

The hypotensive effect of the low sodium diet, in which the daily salt intake must not exceed 0.5 g. (200 mg. sodium), had fallen into disuse in the past owing both to inadequate salt restriction and to the monotony of the diet. The hypotensive action of the rice diet was due to its low salt content, and the claims of Kempner have been confirmed in a Medical Research Council trial: 70% of the cases investigated had described symptomatic relief; in addition, improvement of retinopathies and regression of electrocardiographic changes had been noted. Salt restriction was contraindicated in the presence of renal failure owing to the persistent sodium loss from the diseased kidney which might result in a severe hyponatraemia. The low sodium diet was rarely practicable for patients outside hospital owing to the difficulty of preparing it at home.

Medical Sympathectomy with Methonium Compounds

Various drugs had been used to induce a medical sympathectomy. Of these ganglion-blocking agents, hexamethonium was the most effective. Tetraethylammonium bromide had too transient an action, and "priscol" had little hypotensive effect. Hexamethonium blocked both the sympathetic and parasympathetic ganglia; the former action caused hypotension, but the latter gave rise to various undesirable effects such as impairment of visual accommodation and dryness of the mouth. Constipation and abdominal distension also might occur, but they responded to neostigmine. Postural hypotension must not be confused with these side-effects, as it was an indication of effective therapy. In the presence of diseased cerebral or coronary arteries, the induction of sudden hypotension might cause thrombosis. Owing to poor absorption of hexamethonium from the gut, the oral dosage must be 10 times greater than that required by parenteral routes; if the bromide salt of the drug was used, bromism might result. In addition, irregular absorption might cause the sudden onset of side-effects. For these reasons subcutaneous administration was preferred. Hexamethonium was not metabolized, but was rapidly excreted by the kidneys. Should renal failure be present the drug must be given in small doses owing both to the reduced rate of excretion and to the danger of aggravating renal failure which would be shown by a further rise of blood urea. If renal function was normal, there appeared to be no danger of deterioration on prolonged administration of the drug.

The patient must be in hospital for the beginning of therapy. An initial dose of 25 mg. of hexamethonium

bromide was given by either intramuscular or intravenous routes; and, if the hypotensive effect was satisfactory, treatment commenced with a dosage of 25 mg. subcutaneously three times daily. Following each injection, the patient usually preferred to remain lying for an hour in order to avoid the effects of postural hypotension, but was otherwise encouraged to be up. Thereafter the efficacy of the drug was assessed by measuring the blood pressure two to three hours after the injection, with the patient in the recumbent and standing positions. Tolerance usually developed early, necessitating an increased dosage, and within two to three weeks the satisfactory maintenance dose was apparent: as much as 750 mg. daily might be required in some cases. The patient was then discharged to administer his own injections, and periodic observations were made thereafter to assess the efficacy of the dosage. The three injections of hexamethonium daily increased the lability of the blood pressure and were not intended to maintain a constant degree of hypotension throughout the 24 hours.

Symptomatic relief was marked, with the disappearance of headaches, dizziness, and nocturnal dyspnoea. Cases had been treated for as long as 15 months, but it was too early as yet to compare the results with those obtained by surgery. Hexamethonium was certainly not the ideal hypotensive agent, but was preferable to the low sodium diet.

Veriloid

Dr. R. KAUNTZE described his observations on the hypotensive effects of "veriloid,"[1] a stable reproducible mixture of alkaloids derived from *Veratrum viride*. The drug acted directly upon the afferent branches of the vagus and the central nervous system, giving rise to dilatation of arterioles in muscles, skin, and the splanchnic area, and constriction of the veins. The resulting hypotension could be reversed by ephedrine intramuscularly. Other actions were bradycardia of vagal origin, which was abolished by atropine, and emesis; the latter might be primarily central or follow the hypotension.

Intravenous infusion of veriloid (1 μg./kg. body weight/minute) for 10 minutes lowered the blood pressure in almost all cases of hypertension, except those in the preterminal malignant phase. Intravenous therapy was useful in hypertensive encephalopathy, but otherwise all patients were maintained on oral treatment. By mouth the maximal hypotensive effect was apparent three to five hours after ingestion. Three or four doses daily were employed, starting with 8 mg. divided equally, spaced at not less than four and a half hours and taken after meals to minimize toxic effects, the chief of which were substernal burning, salivation, hiccup, nausea, recurrent vomiting, and peripheral circulatory collapse. The combination of phenobarbitone with veriloid had been effective in reducing nausea and vomiting. The dosage might need frequent adjustment.

About 60% of hypertensives responded to veriloid orally, but in half of these the therapeutic and toxic levels were so close that the drug could not conveniently be used out of hospital. Thus there remained 30% who responded well to out-patient treatment, but in these the disease appeared to progress, although the tempo might be slowed. The pure alkaloid germitrine was similar in action to veriloid and the nausea proportionately no less.

Mechanism of Postural Hypotension with Methonium

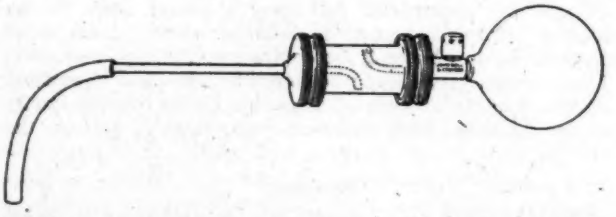
Professor J. MCMICHAEL described investigations which explained the mechanism of postural hypotension caused by hexamethonium. In the normal subject, change of posture from the horizontal to the upright position was associated with a fall in cardiac output, which elicited reflex vasoconstriction to maintain the mean blood pressure. Under the influence of hexamethonium, standing caused the same reduction of cardiac output, but reflex vasoconstriction did not occur, and a profound fall in blood pressure ensued. The effects of this drug, given by injection, on a series of cases was described. Of seven patients with malignant hypertension, three in whom treatment had been begun late had died, but four were now under good control and back at work. Of 27 cases of complicated benign hypertension, 7 had stopped treatment for various reasons, and 18 had responded satisfactorily with objective and subjective improvement. The usefulness of the drug in renal hypertension was also emphasized.

Preparations and Appliances

MUCUS EXTRACTOR FOR USE ON THE NEWBORN INFANT

Mr. H. H. FOURACRE BARNS, gynaecological surgeon, Hospital for Women, Soho Square, W.1, writes: The disadvantages of the ordinary mucus evacuator used for clearing the upper respiratory passages of the newborn infant are: (1) Aspiration of the mucus into the mouth of the attendant, since mouth suction is used. (2) To avoid this contamination of the mouth the attendant often blows out the mucus on to a towel so as to empty the reservoir of the evacuator. By so doing there is the obvious risk of the attendant's nasopharyngeal organisms reaching the end of the evacuator which is to be replaced into the infant's nasopharynx. (3) When using the ordinary mucus evacuator the attendant has to disarrange his face-mask to place the sucking end into his mouth. On occasion this may not be as easy as one would like, and contamination of the gloved hands by the mask may occur.

In order to avoid these disadvantages the mucus extractor shown in the diagram has been made for me by Messrs. John Bell and Croyden, Ltd. The reservoir has a capacity



of approximately 20 ml. It consists of a hollow cylinder with two ends which screw on to form airtight joints. A tube passes through the centre of each of these ends, and in the interior of the cylinder the tubes curve away from each other to form a simple trap device which prevents mucus passing over into the suction mechanism. The distal curved tube is continuous with the cannula to the infant, and the proximal one is continuous with a screw joint for the valve. The suction is produced by a rubber bulb working in conjunction with a small double-ball-valve mechanism. When the bulb is compressed, air passes out of the outlet holes at the top of the valve, and on reinflation it sucks air through the reservoir. The end of the extractor which is to be inserted into the nasopharynx of the infant is covered with rubber tubing, which projects ½ in. (1.25 cm.) beyond the end of the metal. This minimizes the trauma to the mucous membrane. The whole instrument can be held and worked with one hand. It can be wet-heat sterilized, the usual precaution being taken to prevent contact between metal and the surface of the rubber bulb.

The instrument consists of five separate parts—namely, cannula and distal end of reservoir, cylinder, proximal end of reservoir, the valve (which is itself in two parts), and the rubber bulb. It can therefore be cleaned easily.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Doctors' Opinions in Lay Press

SIR,—A number of letters and articles by medical practitioners have appeared in the lay press recently which have attacked or criticized, sometimes with considerable rancour, other sections of the profession. Many of these statements can have done nothing but harm to the general standing of the profession with the public, and it is regrettable that they should have ever been sent for publication.

If a doctor wishes to ventilate a grievance or expound his views on some controversial point, it would be wise for him to do so in such a manner as not to bring his professional colleagues into disrepute. If reflections cannot be avoided, lay journals are not the appropriate place nor lay readers a suitable audience for such matters. The correspondence columns of the medical press are always open to him, and it is there, where any doctor's statements can be checked and if necessary corrected by his professional equals, that such statements should appear.—I am, etc.,

JOHN THWAITES,
Chairman, Central Ethical Committee, British Medical Association.

Treatment of Anaemia

SIR,—I was dismayed to read the letter of Dr. S. Shubsachs (February 23, p. 437), who suggests that there is some merit in adding folic acid to iron pills. No controlled clinical studies are available to show that folic acid is of value in the treatment of iron-deficiency anaemia, and if patients are suffering from pernicious anaemia unknown to their practitioner the haematological picture may be so obscured by the prescription of iron or vitamin pills containing folic acid that the subsequent diagnosis of the patient's disorder may be rendered at least temporarily impossible. Moreover, since folic acid does not prevent the neurological complications of pernicious anaemia, the patient may report to his doctor on account of the symptoms of subacute degeneration of the cord without anaemia. Instances of this nature have already occurred where pernicious anaemia patients who did not know that they suffered from the disorder made a regular habit of eating vitamin pills containing folic acid. Quite apart from the inherent dangers of prescribing such preparations it should be realized that the ordinary ferrous sulphate preparations cost less than 2s. per 100, whereas one of the popular preparations containing folic acid costs more than £1 per 100.

I was interested, too, to read the excellent article by Drs. Nancy Benstead and G. W. Theobald (February 23, p. 407), in which they show no better haematological results from ferrous sulphate tablets containing molybdenum than from those without it. So far as toleration of molybdenized ferrous sulphate is concerned, the following note may be of interest.

In 1948 Messrs. Glaxo kindly prepared for me some tablets of ferri. sulph. co., each of which contained, in addition to the usual ingredients, 3 mg. molybdenum sesquioxide. These tablets were white. Like Drs. Benstead and Theobald, I found that patients who could not tolerate "fersolate" tablets on account of alimentary disturbances were able to tolerate the ones containing molybdenum. I then asked Messrs. Glaxo to provide tablets identical with fersolate but coloured white. These tablets were given to 16 patients who were quite certain that they could not tolerate fersolate, and in 14 of these patients, more than half of whom were in hospital, the white tablets that were otherwise identical with fersolate were tolerated without difficulty. No alteration was made in dosage. The colouring matter added to fersolate tablets is an aniline dye used in the strength of 240 gr. to 600,000 tablets, and it can hardly be held responsible for the symptoms of intolerance of which the patients complained. It is difficult to see how the difference in tolerance can be due to anything other than psychological causes.

—I am, etc.,

Edinburgh. R. H. GIRDWOOD.

SIR,—In their interesting survey of doctors' prescriptions (February 9, p. 292) Professor D. M. Dunlop and his colleagues refer to "shot-gun" preparations of iron, with folic acid, liver, or hog's stomach. They add the comforting statement that these combinations of substances are prescribed only rarely, though it is possible that analysis of "private" prescriptions might reveal a higher proportion.

Dr. S. Shubsachs (February 23, p. 437) and Dr. W. N. Leak (March 1, p. 484) infer that patients with iron-deficiency anaemias improve more rapidly when iron is administered together with folic acid. Since they do not offer any proof, one can only hope that their remarks are not indicative of a widespread prejudice in favour of such blunderbuss "haematinics."

No doubt the travellers in these commodities are very persuasive, and the attractive titles of the preparations suggest a benefit greater than that to be expected from time-honoured remedies, while the prescriber may be influenced by the common fallacy of confusing expense with value.

Whatever the reasons for their continued though, one hopes, limited use, I feel that it is time for the positive disadvantages of such preparations to be pointed out.

1. They obscure diagnosis. Since the preparations contain several substances, each of which would be capable, in *adequate* dosage, of curing different types of anaemia, the incentive towards making a correct diagnosis is lacking. If a temporary improvement, often called a "cure," results, the nature of the original anaemia remains obscure. In the case of pernicious anaemia even after discontinuing treatment the blood picture may be misleading for a considerable time, and both patient and doctor be lulled into a sense of false security.

2. The dosage of each of the constituents is inadequate to produce good results (with the possible exception of iron). The quantities of liver, yeast, and hog's stomach are too small to be of any therapeutic value, and their inclusion must be regarded simply as groundbait, whereas the inclusion of folic acid is positively dangerous. Patients suffering from pernicious anaemia and partially treated with folic acid are exposed, in a small proportion of cases, to the real risk of developing subacute combined degeneration of the cord.

3. These preparations are expensive. Iron-deficiency anaemias, that is, the only anaemias in which such combinations of substances can be given with safety, or with anything approaching adequate effect, are curable by cheaper and better methods.

—I am, etc.,

Bristol. J. NAISH.

What Doctors Prescribe

SIR,—The original article (February 9, p. 292) and subsequent letters have made thoroughly worth-while reading. Particularly those of Professor Dunlop, and the findings of the general practitioners, show a hope of future co-operation. Were a professional panel to produce annually, at the Ministry of Health's expense, a supplement of new drugs of proved worth therapeutically and economically for distribution to general practitioners, these gentlemen would be spared much anxiety and time, the State much expense.

I submit that the idea is not original. Its initial limited application to one of Professor Dunlop's areas would be ideal to test its practical value.

Subsequent alteration in prescription costs for the area could be readily seen. More important still, the general practitioner's constructive criticism would be available.—I am, etc.,

London, S.W.3. D. D. MACDONALD.

SIR,—Professor Robert Platt's remark about his "healthy contempt for most of the pharmacopoeia" of 1920 (March 1, p. 484), and the article by Professor D. M. Dunlop and others (February 9, p. 292), raise problems which have been

discussed repeatedly in this *Journal*. The understanding and treatment of organic diseases have progressed rapidly. We have powerful drugs and we can therefore afford to discard many pharmacological substances, the use of which could be excused as long as we had nothing better to offer to our patients. Yet many teachers of pharmacology continue to teach the use of outmoded drugs, and the students have to learn them. Most students are so impressed by the progress in the treatment of diseases that they are insufficiently prepared when in general practice they are called upon to treat patients who suffer from minor ailments which one does not often see in hospital and for many of which there is no treatment. In particular does the young doctor find it difficult to wean his patients—on whom he is financially dependent—from the use of drugs which are of no value.

While many illnesses have been wiped out or can be cured when they occur, the number of patients consulting doctors in general practice has not decreased. More and more we are coming to realize that the complaints of many patients can be properly understood only in terms of psychosomatic medicine, and most of these cannot be cured by the physical remedies at our disposal. Yet we are still inclined to behave as if the patients' illusion that health in all its aspects can be bought in the shape of a bottle of medicine or a tablet is correct.—I am, etc.,

Stockport. A. MODEL.

SIR,—The ability to assess the value of a drug requires accurate observation, intelligent interpretation, and unbiased judgment. Our profession is well trained in the first two faculties, and is above the average in the third, but then the average is deplorable. That truly objective judgment is a rarity in man, and virtually non-existent in women, can be seen by considering the variety of opinions one hears expressed on certain standard subjects.

The public's attitude towards medicines is more akin to superstition than to reason, and that this is true for all educational levels shows that education as we know it is not enough. My brother, a bachelor of laws and a solid citizen in other respects, attributes his relative freedom from colds this winter to his daily ingestion of a halibut-liver-oil capsule, despite the fact that his diet is in no way deficient. I have several patients who return year after year for anti-catarrhal vaccine, which they are convinced raises their immunity to colds; and yet controlled experiments in industry and the Services have proved that dummy injections are as effective. A doctor friend avidly consumes all his own samples of multivitamin capsules, and as many of mine as he can lay his hands on. The fact that his wife and children enjoy as good health as he, although denied these dietary embellishments, appears irrelevant.

Every child after the age of 5 should be imbued with a spirit of analytical scepticism, and training in objective judgment should be given a permanent place in school curricula.

Until such time as the public and, much more, the doctors have learned to take a more rational view of pill-swallowing, may I suggest that here is a fertile field for State enterprise? What is wanted is a small range of capsules, in a variety of bright colours, and composed of some inert substance. The vast quantities required would enable them to be produced at negligible cost, perhaps 3d. per 100, and an additional advantage would be that their inert composition would render their exhibition less fraught with incidental hazards such as the gastric upsets and idiosyncrasies occasionally encountered in orthodox therapy. The range of colours would cover all common indications, and doctors would prescribe them in all cases in which no clear indication for drug treatment existed. The name of the preparation desired by the patient would be written out in full, followed by some agreed appellation to denote the dummy preparation.—I am, etc.,

Bridge of Weir, Renfrewshire. MUNGO B. HAY.

SIR,—Two points arise from the letter of Dr. Frewen Moor (February 23, p. 436). First, I also have felt this difficulty in ordering proprietary drugs because I cannot remember the pharmacopoeial equivalent. However, my attention was drawn to the *Index of Modern Remedies* (Mair, 1950, price 5s., published by *The Scottish Chemist*). This is easily accommodated in a doctor's bag and gives full lists of even the most recent proprietary drugs with their presumed action, forms of packing, pharmacopoeial equivalent, and in many cases also the price.

Secondly, with regard to his continuous colds, I presume Dr. Moor has had his sinuses examined. My personal experience is that this was the fundamental cause of such colds.—I am, etc.,

Ayr. W. O. G. TAYLOR.

Test for Anaemia

SIR,—I have seen a good deal of correspondence in the *Journal* lately about anaemia. It is very difficult for a busy G.P. to test the haemoglobin; he has not the time even if he has the instrument and ability. I have been a G.P. for over 40 years, and I know that very few G.P.s do test the haemoglobin. The following clinical test does not seem to be well known—it takes no time or trouble.

Give 30 gr. (2 g.) ferri et ammon. citr. thrice daily after meals. If this does not constipate much or even causes some diarrhoea the patient is anaemic and the iron will do good; if it constipates to the point of marked inconvenience she is probably not anaemic. A very simple test, it can do no harm and is right in 80% or 90% of cases. Sometimes ferri et ammon. citr. causes diarrhoea; if so, add liq. morph. 4 or 5 minims (0.3 ml.) to each dose. Tablets of ferri sulph. exsic. are of no use for this test.

I have used this test for over 20 years and found it most useful in the common anaemia of pregnancy and other anaemias. I discovered this about 20 years ago when I got anaemic and took ferri et ammon. citr., and to my surprise found that it cured my constipation, from which I had suffered nearly all my life.—I am, etc.,

Limpsfield. G. D. LAING.

Salivary Tumour of the Hard Palate

SIR,—With reference to the letter by Dr. A. T. H. Glanvill and Mr. B. Martyr entitled "Interesting Tumour of the Palate" (February 9, p. 329), the following account of a tumour of the hard palate should prove of interest.

A woman aged 62 had a three-years history of a swelling in the hard palate, causing no pain, only discomfort. The swelling, 2½ by 2 cm., was sessile, circumscribed and broad-based, softish in consistence, and there were no glands. Under gas and air the tumour was removed without difficulty in March, 1950. It had slightly eroded the hard palate. The incision was closed by sutures and compression applied. The patient made an uneventful recovery and there has been no recurrence so far. The pathological report was: "Section shows typical mixed tumour of salivary gland type with mucoid change in the stroma. There is no evidence of malignancy, but, as in their salivary counterparts, local recurrence is a possibility."

On looking up the literature I found that in reports of 419 salivary tumours 23 (about 5½%) were in the palate.—I am, etc.,

London, W.1. ARTHUR MILLER.

Shortage of X-ray Films

SIR,—After your masterly leading article (January 12, p. 94) and the letters of your contributors I think we may now safely surmise that there will always—in our time—be a shortage of *x*-ray film. Demand for film can, and must therefore, be reduced.

In the last thirty years many devices have been used successfully in radiography in which expensive double-coated film is not needed. There was no real need in the spacious days to use these devices regularly. In my own limited experience I saw the development of pin-hole minia-

ture exposures from the actinic fluorescence of a screen in the middle 'twenties, and the use of bromide paper in the traumatic surgery of the Palestine fracas of 1935–7.

At the present time the greatest demand for large film is from tuberculosis clinics. In the last few years tuberculosis practitioners have come to rely solely on *x*-ray findings for both diagnosis and progress. It is my contention that the use of full-size film is not in all these cases justified. The original diagnosis may well be on the usual 15 by 12 film. The follow-up, the hordes of contacts, spread over a year or more in most cases, are surely the case for which "mass miniature" came into being. The mobile mass miniature is nowadays but a bus-ride away in most regions.

Casualty and fracture work is efficiently performed on bromide paper, as is follow-up work in orthopaedics; one late film is all that is required in salpingography. In the majority of cases in barium meals, a serial-changer at the radiologist's screening session will give a concrete diagnosis, in good hands, on one film. One tomograph film, after a moment's thought, is as good as all the routine films at blunderbuss levels, in thick structures for which this technique was introduced. I submit that economy should not yet be applied to procedures which still show room for improvement. I instance cholecystography, pyelography, arteriography, and skull work. The amount of film likely to be used for these is trivial. A camera adaptation has been devised in my area which will have the approval of even the most financially embarrassed management committee. Its cost is a bagatelle, its upkeep is that of an amateur's camera, and its construction is within the scope of the hospital handyman. The details will shortly appear in the radiographers' technical journal, for anyone who may be interested.—I am, etc.,

West Norfolk. G. E. CHURCH.

Sterilization of Woollen Fabrics

SIR,—With reference to Dr. H. F. Barnard's paper on the sterilization of woollen fabrics (January 5, p. 21), I can confirm his findings regarding hypochlorite treatment of blankets not being adequately bactericidal. In tests carried out over a period of three months at a hospital laundry it was found that when blankets were washed with soap in the normal way the wash liquors and rinse waters soon became heavily contaminated. Starting with uninfected water and washing one load of 30 blankets, the total bacterial count of the wash liquor was of the order of 1,000,000 organisms per ml. with presumptive coliforms present in 0.01 ml. Next, sodium hypochlorite was added to the wash liquor to give 200 p.p.m. available chlorine together with a synthetic detergent in place of soap, and another load of used hospital blankets washed. Over a period of time only a slight improvement bacteriologically, as compared with results from normal soap washes, was noted. In a matter of seconds the hypochlorite reacts with the wool protein, and there is no available chlorine present to kill micro-organisms.

In direct contrast to this, quaternary ammonium compounds (Q.A.C.), as pointed out by Dr. Barnard, retain their germicidal properties when adsorbed on to woollen fibres, at the same time controlling infection in the wash and rinse liquors. Many types of Q.A.C. can be shown to be effective. An example is tetradecylpyridinium bromide; when adsorbed on to hospital blanket fibres its growth-inhibitory action against *Staph. aureus* can be clearly shown (see Fig.). For practical purposes it is important to remember that if blankets are first washed with soap, as is the common practice, then the bactericidal efficiency of any subsequent Q.A.C. disinfectant rinse will be reduced because the Q.A.C. will to some extent be neutralized by the soap residues in the fabric.

To effect economy in practice it is advisable to use a non-ionic detergent in place of soap. The Q.A.C. treatment may then be applied in the final rinse. Dosage will depend on the weight of blanket fabric washed, the type of Q.A.C. used, and to some extent on the mode of washing. Although the process is perfectly simple it is wise to seek expert advice in the first place and later institute bacteriological control at the hospital laboratory on blanket fibres, wash liquor, and rinses.—I am, etc.,

London, W.1. CHRISTINA M. COUSINS.

A.C.T.H. and Cortisone in Leprosy

SIR,—I have read with great interest your leading article "Cortisone and Tuberculosis" (December 29, 1951, p. 1570), in which you discuss the action of A.C.T.H. and cortisone in tuberculosis, and the difficulties and dangers attending their use in this disease.

I have recently been studying the action of A.C.T.H. and cortisone in the sister disease, leprosy, in which the same relief of symptoms attends the use of these hormones, but in which also their use is attended with difficulties and dangers. The following is a brief extract from a summary report on this subject.

Knowledge of leprosy and its complications ("reaction," acute neuritis, acute eye inflammation, etc.), and of A.C.T.H. and cortisone and their mode of action in other diseases, suggests that these hormones might relieve the acute symptoms of leprosy, which can be very troublesome, but they are not likely to benefit the leprosy itself, and might even aggravate it by diminishing or abolishing the tissue reaction which keeps the disease in check. If these expectations are fulfilled the question arises whether by careful regulation of dose, and by continued or intensified chemotherapy given at the same time, it might be possible to secure the good effects of hormone treatment and avoid the bad ones.

Trials of A.C.T.H. and cortisone in the acute and subacute complications of leprosy have been carried out here. Thirty-eight such cases have been treated and studied during a period of four months.

In all cases the immediate response to treatment has been excellent. Severe "reaction," acute neuritis, and severe eye inflammation have been relieved within a day or two. The cessation of treatment has, however, been far too often followed by a recurrence of the symptoms, and also by the development of other complications, and further treatment has given only temporary relief, followed by complications becoming more severe and more frequent, and definitely indicating an aggravation of the leprosy. All attempts by modification of dosage to prevent this deterioration have failed, and the conclusion is that, in general, the use of these hormones is contraindicated in leprosy.

There are, however, two ways in which these hormones are of great value in leprosy. In sulphone sensitization, with drug fever, dermatitis, hepatitis, etc., which may be so severe as to endanger life, a three-day course of A.C.T.H. or cortisone is enough to set the patient well on the way to recovery, although occasionally a second course is needed; in leprous eye inflammation the local use of cortisone in the form of eye drops appears to be of great value in preventing serious damage and possibly blindness. Neither of these procedures has been followed by an exacerbation of the leprous process. A report is in preparation.

—I am, etc.,

Uzuakoli, E. Nigeria. JOHN LOWE.

Cortisone in Rheumatism

SIR,—Dealing with the complications of cortisone therapy Dr. W. S. C. Copeman and his colleagues in their paper (February 23, p. 397) say: "The preoccupation of many observers with these mild side-effects reminds one of a house-proud woman overconscious of a speck of dust which the visitor has not noticed." Many readers, I feel sure, will disagree with their estimate of the importance of these side-effects. Intestinal perforation and haemorrhage, hypertension, and glycosuria, sodium retention and potassium depletion, the development of a modified Cushing's syndrome

—all these add up to more than a speck of dust. It is, however, with the significance of the complications rather than their severity that I am concerned.

Very often a study of the side-effects of certain forms of therapy reveals a lot about the mechanism of the disease under consideration. I have not myself introduced any form of drastic treatment in disease, but I have witnessed the effects of some heroic, not to say peculiar, forms of therapy in leprosy and rheumatism. A recession of lesions in leprosy—cure of a kind—followed such treatment as intravenous tinned milk, intravenous sodium salicylate, intravenous dyes and chemicals of uncertain constitution, potassium iodide in doses of half an ounce daily, and so on. The author who introduced intravenous tinned milk observed that the patient complained of precordial pain and often collapsed on the roadside where the injection was given. His relatives picked him up and took him home and noticed the recession of lesions in due course. At a recent meeting of the Royal Society of Tropical Medicine and Hygiene at which leprosy was discussed the favourable effects of A.C.T.H. on lepra reaction were mentioned, but I was disappointed to note that there was not a single reference to dye therapy or tinned milk. Really there is no need for authors to blush at the mention of previous drastic treatments in leprosy or rheumatism. The original findings, published in all sincerity, were correct. It often happens that subsequent observers emasculate the therapy in their efforts to avoid toxic effects and so it falls into disuse. But this does not mean that the original therapy did not produce a recession of lesions as well as side-effects. Instead of trying to write down or minimize the value of the complications in each case it would be more profitable to inquire what cortisone and tinned milk have in common.

Before the advent of cortisone I was able to show (*Ann. rheum. Dis.*, 1942, **3**, 89) that all the agents which effected cure in leprosy and rheumatism had some debilitating or toxic effect. We can easily recognize it in a long list of agents known to produce cure or recession of lesions—for example, gold and heavy metal therapy, pregnancy, major operations, toxic and infective hepatitis, and, recently, hypoglycaemia in rheumatism; malaria in general paralysis; hypoglycaemia, electroconvulsive therapy, and leucotomy in schizophrenia; pregnancy, prolonged arsenical therapy, and hypervitaminosis D in psoriasis.

The inflammatory reaction which is the basis of rheumatism and leprosy, and the behavioural reactions of schizophrenia, are dynamic in nature. What is more natural than that they should be toned down or suppressed in circumstances of debility or trauma? We may be deluding ourselves in trying to believe that cortisone has some mysterious endocrinological effect which rights what is wrong in rheumatism and that the side-effects are unfortunate accidents to be eliminated by further experience.

In Dr. Copeman's series nearly half the patients showed some obvious manifestations of hyperadrenalism. The side-effects were reversible, and so, for that matter, was the cure. Other authors have described the same phenomenon, and Sprague (*Amer. J. Med.*, 1951, **10**, 567) goes so far as to say: "... A state of hormonal excess of some degree must be established before a favourable clinical effect can be achieved." When authors record that in a given case the drug had to be discontinued because of side-effects and that relapse followed, they also imply that so long as there was a state of hyperadrenalism there was no rheumatism. There is no evidence of adrenal or pancreatic deficiency in rheumatism any more than there is evidence of vitamin-D deficiency in lupus vulgaris. Cure in these diseases is associated with *hyper*adrenalism or *hyper*insulinism and *hyper*vitaminosis D respectively.

We have, therefore, to consider two propositions. Cortisone cures rheumatism and it produces profound alterations in metabolism; or cortisone cures rheumatism *because* it produces profound alterations in metabolism. The first proposition might reduce the value of the side-effects to a speck of dust. The second brings out their true significance. The cortisone therapy of rheumatism may be more elegant than the tinned-milk treatment of leprosy, but the same factor of debility is quite evident in both.—I am, etc.,

Bristol WILLIAM HUGHES.

SIR,—The report by Dr. W. S. C. Copeman and others (February 23, p. 397) is the most objective and helpful paper published in this country. One expression, however, I would cavil at, the use of the phrase "suppression of symptoms." Surely the arrest of fibroblastic activity and the associated diminution in joint swellings are indicative not merely of symptomatic suppression but of actual therapeutic value, either of cortisone itself or of its power to liberate the repair mechanisms of the body?—I am, etc.,

Sunderland. W. GRANT WAUGH.

Critique of Therapy in Rheumatoid Arthritis

SIR,—The tragic effect of premature publicity on true scientific advance is now nearly complete with the publication of Dr. J. J. R. Duthie's report on "Rheumatic Diseases in the U.S.A." (February 16, p. 341), and so it may be opportune to review briefly the unscientific and often puerile attempts made during the last few years to explain these diseases and the results of steroid treatment by theories which could not be upheld, except by ignoring a wealth of knowledge already verified by past experience. That such a review is necessary I have no doubt, since it is possible that a new therapeutic attack is imminent which, based as it is upon a theory at present unsubstantiated by adequate data, has already led to trial treatment by one of the newer antibiotics with "suggestive" results.

Prior to his paper (*Proc. Mayo Clin.*, 1949, **24**, 181), Hench had expressed the opinion that the pathological changes in rheumatoid arthritis were reversible, basing this view upon the amelioration which often takes place during pregnancy and infective hepatitis. That such improvement takes place is common knowledge, but it is equally true that the disease again advances when the physiological or infective process comes to an end. The same sequence of events occurs in psoriasis, but it is not so widely reported that these diseases may in fact deteriorate, and I have personally observed cases of rheumatoid arthritis and psoriasis in which signs and symptoms were *aggravated* by pregnancy. It is hardly necessary to point out that the scaly patches on the skin in psoriasis are a sign of the disease and not the disease process itself. This distinction is important, since the disappearance of these patches merely removes a sign, leaving the dynamic cause completely unaffected.

The easy acceptance of reversibility, coupled with the dramatic effects of cortisone, led to the belief that the problem of rheumatoid arthritis was near final solution. Selye's work, the importance of which has been obscured by the many and vain attempts made to twist its findings to explain the action of A.C.T.H. and cortisone, led to the popularity of the word "stress" for the aetiological agent. I found it very difficult to get a definition of this term stress, but after much discussion it appeared that "any noxious stimulus" could under certain circumstances fill the bill, with the result that really anything harmful could cause rheumatoid arthritis. Was the popularity of the word due to the fact that it could mean all things to all men—i.e., psychological to the psychiatrist, infective to the bacteriologist, etc.?

But, even so, there were difficulties, since it afforded me no explanation of the fact that rheumatoid arthritis is primarily a disease of women, and I felt that it was carrying feminism too far to believe that they are exposed to the action of stress more than their male counterpart. Again, the ready dismissal of a specific infective agent was difficult to understand, since rheumatoid arthritis carries so many facets pointing to infection. The fact that no such agent has been discovered even after many years of patient research militates not one jot against such an explanation.

Rapidly the picture took shape as cortisone and A.C.T.H. were found to have effects on many other diseases, and so the "collagen group" became the convenient pigeonhole for many of our obscure disease problems, which, although having some common pathological features, nevertheless are quite distinct in their clinical signs and symptoms.

Now and then during the past few years some were heard questioning the basis on which all this superstructure was built, but the chorus of enthusiastic followers of cortisone therapy (swelled from time to time by "fellow travellers" with useless reports on the efficacy of related steroids) denied them a hearing until now, when after a few years' experience with this substance it is realized that the problem of rheumatoid arthritis is as obscure as ever.

I think it will be admitted that after an unbiased perusal of Duthie's report we may conclude that cortisone and A.C.T.H. have no effect whatever on the cause of rheumatoid arthritis.

They are powerful two-edged physiological weapons which can temporarily obscure the signs and symptoms of certain diseases (and incidentally, from another point of view, intercurrent disease), and repair is not a concomitant of the period during which signs and symptoms are suppressed.

Their use as a therapeutic agent is attended by grave dangers (now especially that cortisone can be dispensed in tablet form), and, since cessation of treatment is followed by relapse and often deterioration, restriction of their use is strongly indicated.

It appears that the "collagen group" may be on its way out, but, unfortunately for our patients, only as a term.

Finally, to point a moral, may I refer again to a portion of Duthie's report touched upon in my opening paragraph dealing with the work of Wickelhausen? This worker suggests that organisms of the pleuropneumonia-like group may act as the antigen in rheumatoid arthritis, and then on this assumption proceeds to use "terramycin" as a therapeutic agent. The clinical response to this therapy is listed under three headings: (1) gradual improvement, (2) reactivation after withdrawal of the drug, (3) severe exacerbation after a single dose, thought to be due to the destruction of the organism with the release of antigenic material. Here we have the ingredients of another muddled pie of "suggestive" trials, and I fear that soon a new wave of enthusiasm for this new therapy may develop, leading to numerous papers showing masses of statistically significant results of cure, near-cure, and improvement. Therefore let it be stated now categorically that as yet the role of the pleuropneumonia-like group of organisms in disease is unknown and that they cannot be identified with any particular disease process. Any suggestion, therefore, that clinical observations following the use of terramycin in rheumatoid arthritis have the slightest value as evidence that these organisms have any aetiological significance, and any conclusions drawn therefrom, are completely unwarranted.

To condemn treatment by terramycin does not imply that I deny that the pleuropneumonia-like group can play an important role in rheumatoid arthritis. That they may do so is in my opinion possible, since these organisms have been often found in cases of so-called non-specific urethritis in the male, and when it is realized that in cases of this nature a rheumatoid-arthritis-like complication—especially in those following sexual exposure—is common the inference is obvious. Until, however, it is settled what role, if any, this group of organisms plays in the pathogenesis of disease, let us keep our theories as theories, since much disappointment will result from unfulfilled expectations of a therapy based on such flimsy grounds.—I am, etc.,

London, W.1. F. L. LYDON.

Splenins A and B in Rheumatoid Arthritis

SIR,—May I pick a statistical bone with my good friends Drs. G. D. Kersley, D. Watson, and L. Mandel?

In their letter (February 23, p. 438) they write, "Our mean bleeding-time . . . was 97 seconds (S.D. ±26 seconds, n=95)." This is improper from the point of view of both purity of statistical thought and clarity of expression. Standard deviation (S.D.) "is a measure of the scatter of the observations around their mean" (Bradford Hill). It is measured in the same units as the observations and is a positive measurement. The ± sign after a mean is used to indicate the error of the mean, the standard error or the probable error. The error of the mean should not be loosely confused with the standard deviation of a set of observations. Later in the letter they write, "80 bleeding-times . . . gave a mean . . . for B 201±58." The reader is left confused: does ±58 refer to the error of the mean or the standard deviation?

These comments are not merely of academic interest but of practical importance. Let us examine the figures I have quoted, assuming that all figures after the ± sign refer to standard deviations. The problem is to decide: is the difference between the two means 201 and 97 seconds, that is 104 seconds, significant? The standard error of the difference may be calculated from the formula $\sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}}$, giving a value of 7 seconds. The observer is at liberty to choose any level of significance he wishes. Twice the standard error is usually adopted, meaning the difference would occur by chance only once in every twenty trials. Thrice the standard error would be achieved by chance only once in 370 trials. In the case we are considering the difference of the means is nearly 15 times its standard error. If the samples are regarded as too small for this treatment, Fisher's extension of Student's theorem to the comparison of two means could be applied and a precise measure of the probability of this difference occurring by chance made.

If these workers had had a clearer idea of what is meant by standard deviation and the error of a mean they would have been able to state not only that their results supported "to some extent" Ungar's figures, but to what extent in terms of probability, and saved themselves the labour of considering other methods of investigation. I am reminded of the teacher who asked the student, "What is the bleeding time?" and the student replied, "Five-thirty, plus or minus three minutes."

—I am, etc.,

Flimwell, Kent. GEOFFREY E. LOXTON.

SIR,—With reference to Dr. G. E. Loxton's criticism of our letter published in the *Journal* of February 23 (p. 438) we are well aware that S.D. is a measure of scatter and agree that it would have been more correct to repeat S.D. through the letter in place of the ±. We purposely did not attempt to come to anything but negative conclusions, not because of our inability to work out the standard error, but because of our practical assessment of the method. While we recognize the essential value of statistical analysis of figures, we are of the opinion that the wrongful application of statistics to unsatisfactory experiments may apparently prove what is not true.—We are, etc.,

G. D. KERSLEY.
D. WATSON.
Bath. L. MANDEL.

Treatment of Hypoprothrombinaemic Haemorrhage

SIR,—For many years it has been known that vitamin-K analogues correct the hypoprothrombinaemia associated with certain types of jaundice. The response in these cases is always more rapid when these water-soluble products are given intravenously. Drs. A. S. Douglas and Alexander Brown (February 23, p. 412) have investigated the action of vitamin-K preparations on the hypoprothrombinaemias induced by dicoumarol and "tromexan," and they suggest that vitamin K_1 (2-methyl-3-phytyl-1:4-naphthoquinone) is the only preparation which would act as a reliable antidote if a haemorrhage was to occur during treatment.

With proper laboratory control dicoumarin drug therapy should now be fairly free from haemorrhagic complications. This is no doubt the reason why these workers were unable to furnish us with an example of any such case treated with vitamin K_1. The vitamin is not easily obtained and the mode of administration advocated by them far from perfect. I refer in particular to the large volume of fluid (500 ml. 5% glucose containing 200–400 mg. vitamin K_1) and the length of time for its infusion—that is, 5½ hours.

Haemorrhagic complications during dicoumarin drug therapy are either moderately severe (haematuria, epistaxis) or very severe (cerebral haemorrhage, haemopericardium). The moderately severe cases clear up on withdrawing the drug and administering vitamin-K analogues intravenously. I reported such a case two years ago (*British Medical Journal*, 1950, **1**, 183).

The severe cases of haemorrhage are hopeless and they die in a matter of minutes or a few hours. Drs. Douglas and Brown are optimistic if they believe vitamin K_1 is going to save such cases.

Of all the cases which they treated, in their endeavour to prove the superiority of vitamin K_1 over the vitamin-K analogues, only two could be said to have prothrombin levels which I could consider in the danger zone. Both were on tromexan.

With tromexan there appears to be less need for anxiety until the prothrombin activity is below 10% of normal. I have records of several patients where this occurred, and, on withholding the drug for 24 hours *without any vitamin-K*

analogue being given the prothrombin activity was then found to be over 50%. The two cases alluded to would appear to have reacted in a similar way.

On the other hand, when patients on dicoumarol are found to have a prothrombin activity in the region of 10%, although no haemorrhage has occurred, I have found vitamin-K analogues of value. The dicoumarol is withheld and a small dose of one of these analogues given intravenously. This has always prevented a further fall in prothrombin activity, and in fact an increase to a level of about 20–30% is found next day. The dicoumarol treatment is then continued with carefully graded maintenance doses.

I am afraid the advantages predicted for vitamin K_1, alas, can be evaluated only when a case on dicoumarin drug therapy, complicated by a severe haemorrhage, is treated with this new antidote.—I am, etc.,

Manchester. H. LEMPERT.

Habitual Abortion

SIR,—Dr. D. C. A. Bevis (February 23, p. 440) says, "I await with great interest the results of a series of patients treated by Drs. Bishop and Richards with the implantation of inert tablets." This presumably refers to the following sentence in our paper (February 2, p. 244): "There is of course an obvious way of settling the question whether a progesterone implant is endocrinologically or merely psychologically therapeutic—namely, to treat alternate cases with implants of progesterone and an inert compound such as cholesterol." We would like to point out that this does not mean that *we* intend to carry out this experiment—indeed, we do not. It is still our personal impression that a woman who has had two, three, or more previous "idiopathic" abortions before the end of the fifth month of pregnancy stands a better chance of bringing her next pregnancy to a successful termination if she receives a progesterone implant. Whether she stands this better chance because of the endocrinological, psychological, or any other effect of the implant is, to our mind, beside the point.

On the other hand, if there are gynaecologists who genuinely and sincerely believe that there is no treatment that improves the success rate in cases of habitual abortion they would, in our view, be doing a valuable piece of work by implanting alternate patients on the one hand with progesterone and on the other with an inert compound. We believe that this would provide a better index of the part played by psychotherapy (if any) than would be obtained by giving the patients no treatment whatever, as Dr. Bevis and your leader writer suggest. The person who conducted such a study would need to be endowed with an extremely forceful personality if, in these days when even the patient herself has been led to understand by hearsay that there is some kind of treatment for cases of habitual abortion, he can persuade the patient and her doctor that no treatment is better than, or at least as good as, some treatment and can ensure that the patient will not sneak off to another gynaecologist or undergo some form of treatment on the sly.

Even supposing such a strong-willed individual were successful in collecting this no-treatment series, could it be regarded as having satisfied the principles of random sampling and therefore reflect the true incidence of habitual abortion any more faithfully than the figures provided by Eastman and Malpas, about which your leader writer makes the criticism that "though Malpas's and Eastman's figures may have applied to the populations they were studying, they may not, nevertheless, have universal validity"?

It may turn out that the spontaneous cure rate is far higher than has been generally supposed, as your leader writer suggests, but we should be surprised if it becomes an established fact that 85% of women having had two consecutive idiopathic abortions before the end of the fifth month will bring their next pregnancy to a successful termination or that 72% of those who have had three or more consecutive abortions will produce a live baby as the result of their next pregnancy. So long as we can achieve such results, however, following progesterone implantation, we shall consider ourselves morally obliged to continue implanting progesterone.—We are, etc.,

P. M. F. BISHOP.
London, S.W.3. N. A. RICHARDS.

Intra-partum Uterine Rupture

SIR,—I have read with considerable interest the medical memorandum by Mr. Robert Hodkinson (February 9, p. 308).

In a recent case, where rupture of a previous classical caesarean section scar occurred before the onset of labour, the patient was at her home in a state of extreme collapse, but blood transfusion of five pints (2.8 litres) of blood was undertaken over a period of two hours before she was moved. As a result of this her condition was sufficiently improved to make laparotomy and hysterectomy a comparatively safe procedure, and she made a very rapid and completely uneventful recovery.

The point I should like to make is that the firm contraction of the uterus which Mr. Hodkinson mentions was so marked that the uterus was, in fact, turned inside out and complete haemostasis had been secured as a result of this. It would seem, therefore, that if this is a common finding in these patients there should be no question of rushing prematurely into operation, but that they should be retained where they are until adequate resuscitation has been carried out. The uterus, once it has emptied itself of its contents, is likely to arrest its bleeding spontaneously and will therefore allow ample time for transfusion before the patient is moved. It is the moving before resuscitation that is so often fatal in these cases, and attention to this point may do much to reduce the mortality of a very dangerous accident of pregnancy.—I am, etc.,

Worcester. J. A. CHALMERS.

SIR,—Dr. T. F. Redman (February 23, p. 438) and I have no difference of opinion regarding the more serious nature of the spontaneous lower segment rupture as compared with rupture of the lower segment section scar. The latter is a herniation through fibrous tissue, self-limiting in extent—at any rate for some appreciable time—as was so patently shown in the paper by Drs. Dewhurst and Rowley (*J. Obst. Gynaec. Brit. Emp.*, 1951, **58**, 630). The spontaneous rupture is a tearing and separation of muscle fibres, with no limiting boundaries in the uterus. The figures which I quoted in my article (February 9, p. 308) clearly prove that lower segment ruptures (as a group) are more serious than upper segment ruptures. A number of these cases of lower segment rupture do not reach the hospital, and are certified as deaths from obstetric shock, and not until all cases of maternal death are examined post mortem can the full extent of the problem be known.—I am, etc.,

Church Village, near Pontypridd. ROBERT HODKINSON.

SIR,—The following case history bears out Dr. T. F. Redman's comments (February 23, p. 438) on intra-partum rupture in a subsequent pregnancy of a previous lower uterine segment caesarean section scar.

The patient, a married woman of 17, was delivered of her first child by lower segment caesarean section on November 29, 1949, following a trial of labour. The child's head was abnormally large, and, although a mild degree of hydrocephalus was considered to be a possible cause, this diagnosis could not be established until after birth. The birth weight was 9 lb. 5 oz. (4.2 kg.). The mother's pelvis was clinically and radiologically normal. To avoid undue lateral extension of the transverse incision in the lower uterine segment during the delivery of the head a short vertical incision was made into the upper segment in the midline, making the incision T-shaped. This wound was closed in the manner described by Mr. D. G. Wilson Clyne (February 19, 1949, p. 323). There was moderate pyrexia during the first four days of the puerperium, which responded to treatment with sulphathiazole and penicillin. Thereafter the mother's progress was satisfactory and she was discharged on December 18. The child died on February 16, 1950.

The patient became pregnant again at an early date, the expected date of confinement being October 31, 1950. Her pregnancy was uneventful. She was admitted to hospital on November 3. There was no disproportion. Labour began on November 9, following surgical induction. The first stage lasted about five hours. Early in the second stage, by which time the vertex was engaged, a change in the shape of the abdomen was observed. The portion of the uterus below the umbilicus appeared broadened and foetal parts were so readily palpable as to indicate uterine rupture. The patient's condition was good and strong uterine contractions continued. On opening the abdomen the lower segment was found to have ruptured without bleeding having occurred. The edges of the previous wound in the lower segment were separated and the gap bridged by intact membranes. The sac was ruptured and a living male child weighing 6 lb. 15 oz. (3 kg.) was extracted. The tissues of the lower segment were so thin and deficient that there was no safe alternative to subtotal hysterectomy. Both mother and baby made good progress and were discharged on November 26.

—I am, etc.,

Stockport. W. LOVE.

Scientific Exhibition at the Annual Meeting in Dublin

SIR,—We would like, through the medium of the *British Medical Journal*, to draw attention once more to a new feature which is being introduced at the Joint Annual Meeting of the B.M.A. and I.M.A. in Dublin this July.

This will consist of a series of scientific exhibits, each staged in a stand having an open front of about 10 ft. These exhibits will demonstrate the newest ideas in various branches of medicine and surgery and will be open to all members attending the meeting; a member of the profession will be in attendance at each stand to deal with any queries.

The scheme in this, its first year, will necessarily be small in extent, and those wishing to avail themselves of space should apply as early as possible, so that the organizers may make adequate arrangements. The general pattern will follow, on a much smaller scale, the exhibitions held at the annual meetings of the American Medical Association. Originality in display will be welcomed, and charts, drawings, specimens, and other displays can be provided with lighting, which should increase the value of the display. No charge will be made for stands, nor for reasonable lighting.

Full particulars of the stands and details of method of application will be found on page 100 of the *Supplement*.—We are, etc.,

R. A. Q. O'MEARA. M. D. HICKEY.
Dublin. W. J. E. JESSOP. D. K. O'DONOVAN.
Organizing Committee, Scientific Exhibition.

POINTS FROM LETTERS

Prostatic Obstruction and Hernia

Mr. J. CLAPHAM COATES (Hull) writes: Mr. Thomas Moore's medical memorandum (February 16, p. 362) rightly advocates the simultaneous treatment of hernia and the causative prostatic obstruction. Another simple method of attaining the same end is to take advantage of the exposure of the prostate to gain access to the internal aspects of the femoral or inguinal canals as originally proposed by Henry. This adds very little to the operation. Henry's method is a very good one for femoral hernia as a routine, but its value in oblique or direct inguinal hernia is more debatable and I use it for these only where there is associated prostatism. I agree with Mr. Moore that, with modern chemotherapy, the disadvantages are mainly theoretical. Elderly patients are always very pleased to part with two disabilities at one operation.

Pink Disease and Infections in Infancy

Dr. W. J. M. MCLEOD (Belfast) writes: I read with interest Dr. A. S. Cook's letter (February 16, p. 383) on pink disease. Before the advent of antibiotics I saw an infant with typical pink disease well established for six weeks, when it developed whooping-cough. Treatment consisted of vitamin supplements, especially B complex. The whooping-cough proceeded to a moderate attack without complications. In three weeks' time there was neither sign nor symptom of pink disease. In a brief search of the literature at the time I could not find any similar occurrence reported, but did find a statement that in Australia pink disease had been cured by an attack of measles. There would appear to be scope for investigation of the relationship between pink disease and the common infections of infancy by someone able to cast a wide net.

Forgotten Tourniquet

Dr. C. D. SANDERS (Kuala Lumpur) writes: It is nowadays understood that not only shall the person putting on a tourniquet be responsible for timing and also removal of it, but the anaesthetist, as it is put on under his supervision in the anaesthetic room in the majority of cases, shall also share the responsibility, leaving the surgeon, freed of clock-watching, to press on with his task. Various devices, such as egg-timers, stop-watches, and tying the anaesthetist's wrist or gown to the end of the tourniquet tape, have been used, but none are altogether satisfactory. The most satisfactory device I have so far come across is a timer which can be set for any number of minutes up to one hour, and when the allotted time has expired a bell rings. It is attached quite simply to the anaesthetic machine. The obvious advantage of such a timer is that the automatic ringing of the bell informs everyone in the theatre that the allotted tourniquet time has expired.

Medico-Legal

DAMAGES FOR PERSONAL INJURIES

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

In civil actions arising out of personal injury or death the task of compensating the victim in terms of money falls upon the jury if there is one. If there is not it falls upon the judge. Either party can appeal to the Court of Appeal if dissatisfied with the amount awarded, but the Court of Appeal will interfere only if the court below either took into consideration or omitted from consideration something which in law it should not have done, or arrived at a figure which in the view of the Court of Appeal was wholly unreasonable. There is a further appeal by leave only to the House of Lords. Whether such an action is tried at first instance by a judge and jury, or a judge alone, depends on whether either party asks for a jury.

The difficulties involved in assessing a proper amount have been commented on in the Court of Appeal[1] in an action in respect of personal injuries to a boy of 6 who was knocked down by a motor-cycle. As a result of injury to his head his whole personality had been changed, and from a bright intelligent boy he had become irritable and irresponsible in his actions. The court of first instance, sitting without a jury, awarded him £5,000 damages, and the appeal was brought on the ground that the award was inadequate.

The Lords Justices in dismissing the appeal said that in cases of serious personal injuries it was most desirable that damages should be assessed by a jury. To make such an assessment was one of the most difficult tasks which fell to a judge sitting alone. In the past, most such cases had been tried by juries, and then there was a period when insurance companies thought a judge would not be as sympathetic as a jury and juries went out of fashion. Later, insurance companies concluded that a judge was apt to give more damages than a jury, and they became more attached to juries.

Lord Justice Singleton added that in his view the time of the courts would be saved if in cases of serious personal injury damages were assessed by a tribunal composed of three judges of the King's Bench Division. He thought they would reach a decision on a more stable basis than had been reached so far in the assessment of damages, and he thought their decision should be final.

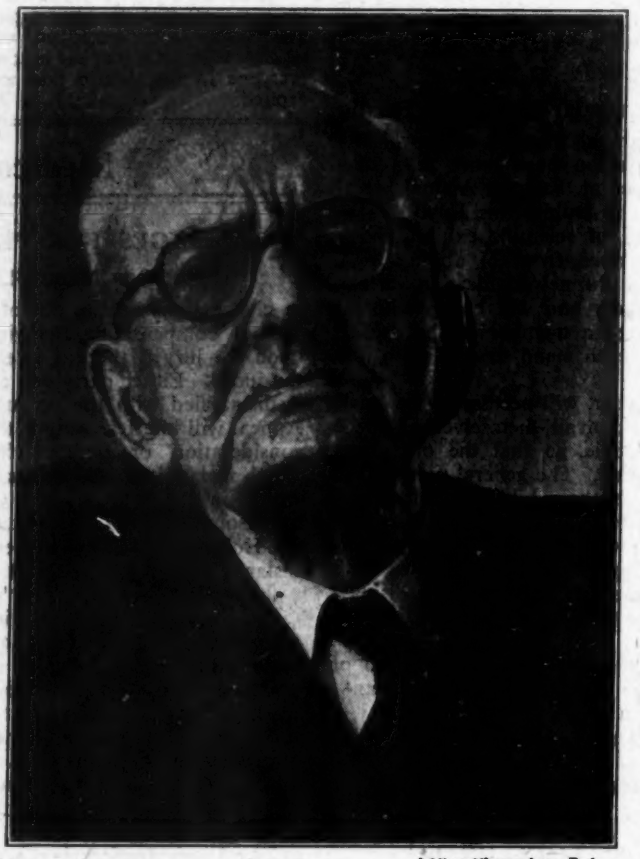
This suggestion should be of particular interest to the medical profession and to the Ministry of Health, because serious personal injuries or death are involved, as the readers of these columns will be well aware, in nearly all actions for professional negligence against doctors and hospital authorities.

[1] *Manchester Guardian*, July 4, 1951.

Obituary

Sir CHARLES SHERRINGTON, O.M., G.B.E., M.D.
F.R.C.P., F.R.C.S., F.R.S.

The death on March 4 of Sir Charles Sherrington at the age of 94 is the passing of the man of genius who laid the foundations of our knowledge of the functioning of the brain and spinal cord. His classic *Integrative Action of the Nervous System* (1906) is still a source of inspiration to physiologists all over the world; it was reprinted as recently as 1947 for the first post-war International Congress of Physiology. His work did for neurology what the atomic theory did for chemistry. Neurones were shown to be the functional units of the nervous system, and their orderly interaction on one another through synapses—a term he invented—formed the basis for understanding of reflex action and of many common clinical conditions, such as tabes dorsalis and hemiplegia. He received many honours, including the Order of Merit in 1924, and in 1932 the Nobel prize in physiology and medicine jointly with Dr. E. D. Adrian.



[Allan Chappelow, B.A.

Charles Scott Sherrington was born in London on November 27, 1857, and educated first at Ipswich Grammar School. He then began his medical studies at Edinburgh, but was soon transferred to Cambridge to be with his brother, and he entered Caius College, where he was later to be a Fellow and then an Honorary Fellow, in 1880 when he was nearly 23. At this time the notable part of the Cambridge Medical School was the physiological department, which had been built up by Sir Michael Foster and which contained such men as W. H. Gaskell and J. N. Langley, both working on the physiology of the nervous system. In fact Sherrington published his first scientific paper with Langley in 1884, the year in which he went down to begin his clinical studies at St. Thomas's Hospital, and the subject was a histological study of the brain of a dog on which F. L. Goltz, of Strasbourg, had previously demonstrated the physiological effects of decortication. Before he qualified M.R.C.S. in 1885 he had also found time to go to Alsace for a brief while to work with Goltz.

At this formative period he was not yet committed to neurology. In the summer of 1885 he was sent by the Royal Society, with C. S. Roy and J. J. Graham Brown, to study a cholera epidemic in Spain, and in the following year for a similar purpose to Italy, afterwards going on with his necropsy material first for two months to Virchow's laboratory in Berlin and then transferring to that of Robert Koch, where he stayed nearly the whole of 1887. During this time he attended courses on bacteriology and histology, including one by Waldeyer, who in 1891 was to establish that the nervous system was composed anatomically of discrete microscopic units, the neurones. He also worked for a month with the experimental physiologist Zuntz. When he returned to London towards the end of the year he was appointed lecturer in physiology at St. Thomas's Hospital.

Anatomy, pathology, and physiology were not then so completely separated in thought and practice as they are to-day. Sherrington's only paper in 1888 was on the pathological anatomy of a case of locomotor ataxy. The following year he published among other work some observations on the formation of scar tissue and the processes of healing, and in 1891 his publications included two in the *British Medical Journal*, "Note on Some Functions of the Cervical Sympathetic in the Monkey," and "Note on the Nerve Supply of the Bladder and Anus." At the same time he was interested in leucocytes, and in measuring the blood volume, but his principal effort remained in neuro-anatomy and neuropathology, and for this his foreign experience was very valuable. Even the cholera investigations were not wasted, since through them he had met the Spanish neuro-anatomist Ramón y Cajal, and the Italian Golgi.

In 1891 he was appointed professor and superintendent of the Brown Institution in succession to Victor Horsley. This was a veterinary hospital (destroyed during the 1939–45 war) intended for the prevention of cruelty to animals, and Sherrington was able to experiment on the animals under the terminal anaesthesia which was humanely and mercifully destroying them. Now at the age of 34 he began his classical researches by making a systematic study of the effects of cutting the dorsal and ventral spinal nerve roots in cats, dogs, and monkeys, discovering their segmental distribution and mapping the sensory dermatomes, which are similar in monkey and man. He found also that one-third to one-half of the nerve fibres passing to a skeletal muscle are sensory nerves, and not all motor nerves as hitherto assumed, and that they were linked to the muscle spindles previously described by Golgi. This was the discovery of a new sense, proprioception, and led to the understanding of tendon reflexes such as the knee-jerk, and the classification of the pathological physiology of such diseases as tabes dorsalis, where the spinal tracts carrying the proprioceptor impulses are damaged. It led on, also, to

the study of the reciprocal innervation of antagonistic muscles and their reflex interactions—work now a commonplace of elementary teaching in every medical school. A second line of work was the precise mapping of the motor area of the cerebral cortex in monkeys, with the effects of stimulation and ablation of different parts of it, which led to the understanding of decerebrate rigidity as the free play of lower brain centres released from cerebral control, and hence to the explanation of the signs of hemiplegia.

This work was continued and developed when Sherrington moved to the Holt chair of physiology at Liverpool in 1895. Much of it was brought together and interpreted in the *Integrative Action of the Nervous System* (1906), henceforth a classic. In 1913 he left Liverpool for the Waynflete Chair at Oxford, and took up the more detailed analysis of individual reflexes, in particular the stretch reflex by which the tone of an individual skeletal muscle is maintained in response to stimuli from the stretch sense organs in its own substance. This and much other work was summarized in *Reflex Activity of the Spinal Cord* (1932), written jointly with his collaborators, J. C. Eccles, E. G. T. Liddell, D. Denny-Brown, and R. S. Creed. He retired from the chair in 1936, at the age of 79.

In addition to his neurophysiological researches Sherrington made special investigations for various bodies, including the B.M.A. (effects of chloroform, 1902–6) and a number of Government Departments, and found time to take an interest in school hygiene, and to sit on many official committees (sight tests, 1910–12, factory lighting, 1913, etc.), and to act as chairman of the Industrial Fatigue Board (1918) and of the committee on Foot and Mouth Disease (1924). He also served a term on the Medical Research Council. Very many honours and distinctions came his way. He held honorary doctorates of 21 universities throughout the world, and was an honorary fellow, member, or associate of over 40 academies. He was a president of the Royal Society and a Royal and Copley medallist, an honorary F.R.C.P. (1912) and F.R.C.S.Eng. (1921), and a president of the British Association (1922, the year in which he was created G.B.E.). He became a member of the British Medical Association soon after qualification, and served as secretary of the physiology section (London, 1895), vice-president (Ipswich, 1900; Toronto, 1906), and president of the anatomy and physiology section (Belfast, 1909). He was quite a frequent contributor to the *British Medical Journal*, a special issue of which (November 22, 1947) was produced to celebrate his 90th birthday, and his last contribution was an appreciation of Goethe (1949, 2, 449).

The Integrative Action of the Nervous System provided above all a set of concepts by which the nervous system could be understood. In his Gifford lectures, published as *Man on His Nature* (1940; second edition with bibliography of all his writings, 1947), Sherrington expanded his philosophical outlook to consider the place of mind in the universe. This discussion was partly historical, and part of it was further elaborated and considered in *The Endeavour of Jean Fernel* (1946). The elaborate care with which these books were written illustrates his interest in words, which found another expression in the writing of poetry, some of which was published in 1925 in *The Assaying of Brabantius*. The reading of Spanish literature was a by-product of his expedition of 1885, and he had a wide acquaintance with many literary by-paths, and with painting and architecture. As an undergraduate he had played for his College XV, and been a mountaineer, in spite of short sight. He married in 1892. His wife died in 1933, and they are survived by one son.

We are much indebted for the following appreciation to Dr. E. D. Adrian, O.M., P.R.S.: Sir Charles Sherrington retired from active work in the laboratory 17 years ago. Since then his Gifford lectures, *Man on his Nature*, and his book on Fernel have had wide recognition from a public knowing little of the nervous system, and he has been thought of more and more as our foremost authority on the development of biological ideas, on man's interpretation of his experiences. So he was; but he is the scientist's philosopher because he had advanced natural knowledge himself by skilled observation and experiment, by 50 years' unremitting work in the laboratory, and because his own interpretation of his discoveries had given a new extension to the biologist's outlook. Physiologists will know this well enough. To those who have had to struggle with the mass of detailed material about the brain and cord Sherrington's *Integrative Action of the Nervous System* brings order out of chaos: it is hard reading at first, because every sentence is charged with meaning, some of it direct enough, but some reaching out to half-formed pictures of a wider landscape. Though it was published in 1906 it is still as refreshing as it was then. It has needed no revision, but Sherrington's experimental work went on at high pressure for another 30 years, filling in the gaps and strengthening the framework.

He had a mastery of all the technique of mammalian experiment, so that no laboratory in the world could vie with the standard he set at Liverpool and Oxford, and he was an acute observer who could see all that was happening outside the immediate range of his experiments. But it is very seldom that such a brilliant experimental skill is combined with such an appreciation of wider bearings. He studied the spinal reflexes, and through them he came to the picture of man reflecting on his nature.

It was always a great privilege to listen to his talk, for he had a store of vivid reminiscences about the events of his long scientific career, about his mission to Spain in 1885 to study the cholera epidemic, his dinner with Pavlov in Leningrad in the troubled times of the Tsarist regime, his work at the Brown Institute, and all the notable people he had met. And his stories of these remote times, seldom repeated and never without some fresh detail, were the stories of a man who was a scientifically trained observer of persons and things but was never without a kindly tolerance and wisdom. He faced life with a deep humility and no malice: he could be indignant at insincerity and pretentiousness and at the abuse of authority, and he was an effective councillor and administrator because his modesty did not prevent him from speaking his mind. But his poetry and the books and lectures he published after his retirement show most clearly why he was so well loved. Even in his strictly scientific writings he could not conceal his charming flashes of humour, his lively imagery, and his wide range of knowledge, but it is in some of his shorter poems and in his occasional lectures that Sherrington is revealed most clearly.

The lecture on Goethe which he gave at Lady Margaret Hall in 1942 is a good example. He took great pains to be fair to Goethe as a scientist and published an expanded version of the lecture seven years later. The opening sentences could not have been written by anyone else. They show not only Sherrington's tricks of language and construction but how tellingly he could use them. "Two facts we may, at outset, recall about Goethe. Poet though he was, he was yet lifelong an ardent student of the sciences of Nature. And this other, that with him—not merely as usage of the German language—Nature was usually Nature with a capital N. The thoughts of few men can be more liberally on record than are Goethe's, biographically and autobiographically, in his formal views and in his correspondence. We may look therefore to exceptional opportunity of knowing what this Nature with a capital N stood for in his mind. He would have wished us to know."

Sherrington the scientist, in spite of all his courtesy and tolerance, cannot quite bring himself to stomach Goethe's setting himself up as a greater Newton, but Sherrington the poet could not resist the pleasure of quoting Goethe's verse or withhold admiration for his courageous acceptance of the world. Sherrington's acceptance of the world was that of a man of essential humility, realizing all the limitations of the human intellect but finding a constant encouragement as his researches brought him closer to what is at least one aspect of the truth. He was puzzled by the problem of mind and matter, a real problem to him and not a verbal quibble, but he had found an absorbing interest in both sides of the picture and he was grateful that his friends took such a kindly view, so he would have described it, of what he had done.

Dr. F. M. R. Walshe, F.R.S., writes: To his physiological colleagues and pupils we may leave the just description of Sherrington's contribution to their science, the appreciation of what these have meant to physiology, and also—and perhaps even nearer the heart—the expression of their deep sense of the lustre he has conferred upon the British school of physiology.

There remains to be given to his memory a tribute of affection and admiration not less sincere or gladly given from the body of clinical neurologists. It would be difficult to overestimate the inspiration he has been to clinical neurology, or the influence his work and genius have had upon neurological thought throughout the world, but perhaps first and most deeply in his own country.

There is perhaps something singularly appropriate in this, for it was from a clinical neurologist, Hughlings Jackson, that Sherrington himself derived no little inspiration. The very phrase, "Integration keeps pace with differentiation," that we associate with Sherrington, and that we find implied in the title of his classic work, *The Integrative Action of the Nervous System*, he took from Jackson, and he has returned to neurological medicine in overflowing measure the gift he got from its most distinguished exponent.

Those who are familiar with neurological literature during the early years of the present century will find that neurology had in that period departed somewhat from the close and fruitful association with experimental neurophysiology that it had enjoyed during the last quarter of the nineteenth century. Largely under Continental influences, it had become predominantly nosographical in methods and interests, and the steady growth of new knowledge and the discovery of new diagnostic signs were not being accompanied by a corresponding analysis and interpretation of these phenomena in physiological terms. For example, the florid and purely descriptive terminology that grew up around the study of cerebellar syndromes—based upon no scientific principles, telling us nothing of cerebellar functions, but showing wholly undeserved powers of survival in the literature—illustrates the contemporary outlook of the period, and another example of this was the crop of eponymous signs and syndromes that developed like unsightly weeds in neurological writings. Then, during the second decade of the century, the influence of Sherrington's work began to show itself in clinical neurology in this country, a little later in America, and still later and haltingly and imperfectly on the Continent. Physical signs hitherto regarded purely empirically began to find interpretation in terms of physiology. The familiar Babinski plantar response was found to be an integral part of Sherrington's nociceptive flexion reflex, the hypertonus of upper motor neurone lesions was qualitatively identified with decerebrate rigidity. Later the work of Magnus and de Kleijn, an offshoot of Sherrington's school, provided the elucidation of other clinically observed phenomena. This process of rationalizing symptomatology has gone on steadily and is not yet ended, and the face of clinical neurology has changed remarkably in our time under the living influence of Sherrington's work. Nor is this all, for the carrying over of animal physiology to man makes its own contribution to physiology.

But it is not for this alone that neurologists will remember Sherrington, it is not only as one of the master builders of modern neurology that he has gained our regard. All those who have had the privilege of knowing and working with him, or have sought his assistance in their problems, will recall his sympathetic interest and his unstinted generosity in time and effort, and not less the thousand and one kindnesses he so unobtrusively and thoughtfully rendered them. Great as was his scientific achievement, he was far greater than his work, and it has been given to few men to command the intense warmth of affection and regard that Sherrington aroused in all who had the privilege of his friendship.

In his writings, whether purely physiological or philosophical as in his Gifford lectures, Sherrington's literary style was all his own, and, difficult as it sometimes was, it nevertheless came to have a fascination for those who knew it and appreciated its essential clarity. Some of his verbal coinings have permanence and have taken their place in nomenclature, and of these the term "synapse" is perhaps the most familiar example.

As we survey in retrospect the vast mass of his writings, perhaps one small disappointment remains—namely, that in his Gifford lectures he came to rest upon so negative a position in respect of the problem of the relationship of mind to the nervous system. Some cannot believe that this is the last word on the subject, even the final word that could be uttered in the present state of knowledge. Yet his conclusion will satisfy many as being more prudent than the false simplicities of those who say that the problem is a phantom one and evade its difficulties by saying that it does not exist. The problem is not yet solved, nor within sight of solution, and it is surely better that he should have said so than that he should have had recourse to an easy dialectic that is no substitute for knowledge.

If we have to sum up the lesson of his work for science, surely it is that he combined in it a perfect balance of accurate observation and the capacity to ask the right questions of Nature with an imaginative and logical synthesis of the facts that in sum constitute the true quality of scientific genius.

Professor J. C. Eccles, F.R.S., writes: The impact of the news of Sherrington's death left his friends a tragic sense of personal loss. There was a sudden realization that one could no longer communicate with that mind of unsurpassing versatility and vigour. I recently returned to England after nearly 15 years' absence and expected that Sherrington would be changed beyond all recognition, on account of his physical disabilities. One approached him with some misgiving and apprehension. But immediate reassurance came on hearing him speak. Here was the same person that we had known and loved still speaking from that aged and disabled body. There was even at times that bird-like quizzical look, that sharp understanding, and there was as always that solicitude for friends.

We should try to see his life in the long perspective of years as the unity that it was to him. For nearly 50 years there was that amazing performance as a scientific investigator. We can now only faintly realize the labour and insight that were required in order that the prevailing vagueness and confusion should be reduced to those clear principles on which modern neurology is so securely based. One thinks at random of synapse, convergence, and the final common path, the motor unit, algebraic summation of the excitatory and inhibitory influences on the motoneurone.

But throughout all this detailed analytical study he never lost sight of the behaviour of the whole animal and that ultimate of all human problems: What is the nature of man? It can be said that in the last two decades of his life he was obsessed with this problem, for he returned to it again and again. He knew that many of his friends and colleagues had not accepted his dualistic view of man. Only nine days before his death he spoke to me at length, and I can recall some pertinent fragments. "My writings on dualism have not been well received; they have found a

very unfavourable climate of opinion." "X thinks Nature is very simple, but it is not like that." "For me the ultimate reality is the soul of man."

I would venture to suggest that had he lived longer he would soon have seen the climate of opinion growing more favourable, a change that would be largely due to his own pertinent arguments for the reality of both the body and the mind of man.

Medical Notes in Parliament

LORDS' AMENDMENTS TO DENTISTS' BILL

The House of Lords on March 4 went into Committee on the Dentists' Bill.

Lord WOOLTON moved to insert a provision that the General Dental Council could direct that a person who had passed examinations required to obtain a foreign diploma should be treated as a person holding a foreign diploma. He said this was designed to prevent hardship to about 30 foreign dentists in the United Kingdom who, although they had passed their examinations in the country where they were trained, had been deprived of their diplomas for political or religious reasons. Lord JOWITT suggested that refugee Jewish dentists who had fled to Britain from the Hitler tyranny and had not practised dentistry for a considerable time might require some kind of refresher course. He presumed there was power for the General Dental Council to impose such a course. Lord WOOLTON agreed to look into the matter, and the House approved the amendment.

Lord SILKIN moved to insert a provision instructing the General Dental Council, within 12 months after the coming into force of the clause, to make regulations for the establishment of dental prosthetists. These were defined as dental technicians with special qualifications to undertake the fitting, insertion, and fixing in the mouth of dentures, artificial teeth, and other oral dental appliances. He said the prosthetist would be permitted, with proper supervision, to take the impression in the mouth, to fit the denture, and to complete the job. The framers of the Bill had left it to the General Dental Council to decide whether or not regulations should be made in any particular category of dental auxiliaries. He proposed that it should be obligatory upon the Council to make regulations setting up this class. He realized that the amendment would not be welcomed by the dental profession, who had made public a number of objections to it. It was expected that some 2,000 technicians would undergo the necessary training to permit them to become registered as dental prosthetists.

Lord WEBB-JOHNSON urged the Government not to accept the amendment. To allow technicians to do work which should be done by qualified dentists was not justifiable. When there were dangers in carrying out a procedure that procedure should be in the hands of a qualified professional man. Badly fitting dentures might lead to loss of other teeth and to serious disease of the gums. He had seen several cases of cancer produced on the gum by badly fitting dentures. The right body to decide whether a special ancillary class should do this work was the General Dental Council.

Lord WOOLTON could not accept the amendment. He had discussed the matter with Mr. Crookshank and had no reason to think that the Minister was likely to alter his mind.

The amendment was withdrawn. The House accepted another amendment, proposed by Lord ONSLOW, to make it clear that ancillary dental workers, while permitted to work as such only in specified services, might, if qualified to do another kind of ancillary work (for example, that of an oral hygienist), be permitted to work in that wider field. On the motion of Lord WEBB-JOHNSON the House accepted an amendment providing that dental auxiliaries should be permitted to extract only deciduous teeth.

Dental Companies

A long amendment dealing with the right of appeal of dental companies to the Privy Council against the decision of the General Dental Council to end their right to continue in the business of dentistry was proposed by Lord WOOLTON and accepted. He said the Government considered that the growth of such companies was rather undesirable. Since the National Health Service started 37 new dental companies had come into existence, and the total was now 62. The majority were small companies, employing one or two operating staff.

Lord WOOLTON promised to look into the nomenclature of dentists and ancillary workers before the report stage. Lord WEBB-JOHNSON reminded him that anyone who attempted to persuade the public that he was a qualified medical man when he was not was subject to penalties. For the protection of the public the titles of dentist, dental surgeon, and dental practitioner should be equally protected. Lord WOOLTON said protection was already given by the Act of 1921.

Tuberculosis in Tyneside

Mr. EDWARD SHORT on March 7 said that in 1919 the incidence of tuberculosis of the lung was much the same on Tyneside as in the rest of England, but that in the following 20 years the rate for England and Wales was halved while the rate for Tyneside dropped only slightly. From 1939 to 1949 the rate for Newcastle-upon-Tyne and most of the Tyne area became almost double the national level. Since the war there had been a great improvement, but the relative position between Tyneside and the rest had not improved at all. It nearly reached the high level of incidence in Scotland, which had been mentioned by Mr. Walter Elliot in an article in the *British Medical Journal* (1949, 2, 297). Mr. Short mentioned that the position for lung cancer was now nearly as bad as for pulmonary tuberculosis. Various reasons could be adduced for this. There was a very large child population and the schools were overcrowded. There was a large Irish population. The new tendency in the North-east for married women to remain at work might have increased the figures. But the greatest single factor in the Newcastle area was poor housing. By the standard of the Housing Act, 1936, more than 20% of the population of the city were overcrowded. Night sanatoria might help—they had been tried successfully in London—and there was also a question of hostels for children living in infected households.

Miss PAT HORNSBY-SMITH said the number of deaths from tuberculosis on Tyneside was half that of 20 years ago, despite a rapid increase in population. Deaths from respiratory tuberculosis in Newcastle-upon-Tyne were 227 in 1945 and 183 in 1950, a reduction of one-fifth. In Northumberland the figures were 186 in 1945 and 124 in 1950, a reduction of one-third. The figure for the whole of England and Wales over the same period showed a reduction of one-third. The figures for 1951 were not wholly available, but there was in general a substantial reduction in tuberculosis mortality. Tyneside figures were higher than those for some other areas, but were being progressively reduced. Figures for notification did not fall so fast, because increased numbers had been detected by mass-radiography.

Doctors' Cars.—Mr. Peter Thorneycroft informed Dr. Stross on March 6 that he was still considering representations made by the British Medical Association that some doctors could not find the money to pay a deposit of one-third for purchase of a motor-car and the remainder in 18 months.

Dr. Kroll.—Mr. Crookshank assured Mr. H. Hynd on February 28 that all suitable treatment for patients with certain brain injuries was already available within the National Health Service, and there was therefore no need for them to be sent to Dr. Kroll in Germany.

Vital Statistics

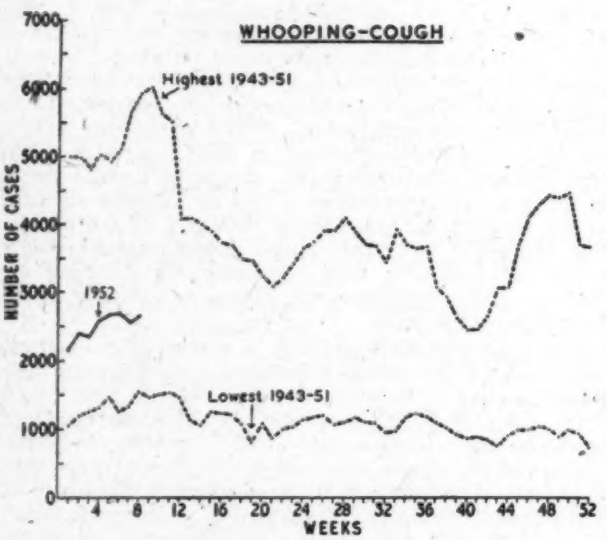
Smallpox in Lancashire

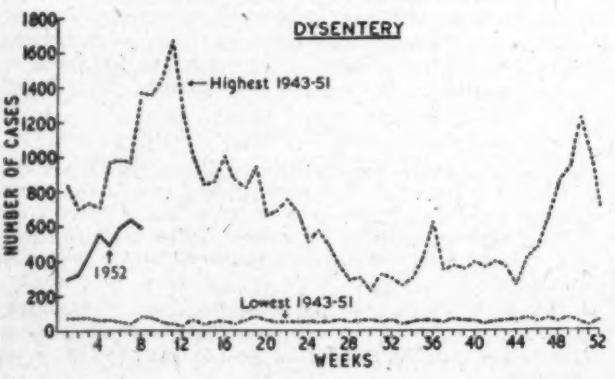
The diagnosis of variola minor is certain, and there have been no deaths. There was a flurry of cases at the beginning of March, but in the past few days the incidence has fallen. The disease is confined to Rochdale, apart from a few patients resident in neighbouring districts who were infected in Rochdale. In Littleborough U.D. the first case to be recognized was in an unvaccinated child who had been in contact with a patient in Rochdale but was not under surveillance. He sickened on March 1, developed a rash on March 5, and was removed to hospital on March 7. There are no reports of the disease in any other part of the country.

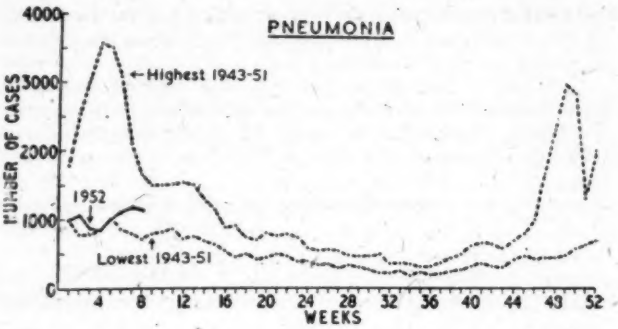
Notifications of smallpox received by the general register office this year are as follows: in the week ending February 16, 1; February 23, 18; March 1, 7; and March 8, 62.

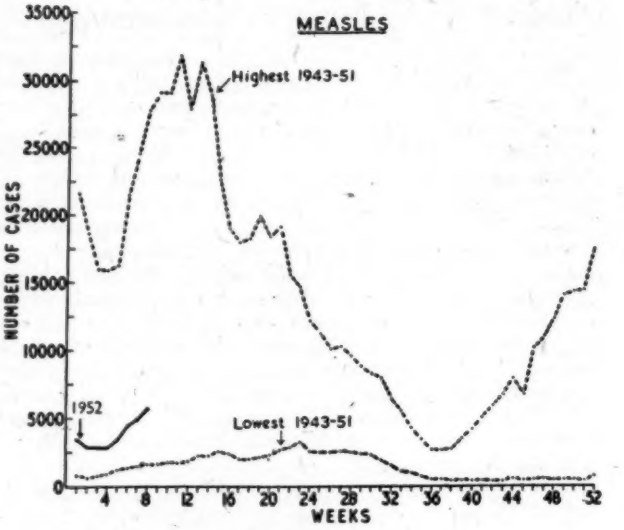
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1943–51 are shown thus --------, the figures for 1952 thus ————. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

During the week ending February 23 an increase was recorded in England and Wales in the number of notifications of measles 754, scarlet fever 132, and whooping-cough 98, while the largest decline was 45 for dysentery.

A small increase in the incidence of measles was recorded in most parts of the country. The largest rises were Lancashire 191 and Durham 173. The variations in the local trends of scarlet fever were small; the only exception was a rise of 41 in Lancashire. The rise in the incidence of whooping-cough was due to the experience of the southern section of the country, while in the north a small fall was reported. The notifications of diphtheria were 11 fewer than in the preceding week; the chief feature of the returns was a decline of 8 in Lancashire. Almost one-half of the diphtheria cases in the country were notified in three towns —Lancashire, Darwen M.B. 6; Warwickshire, Birmingham C.B. 5; and Devonshire, Plymouth C.B. 4.

The 18 cases of smallpox were notified from Lancashire, Rochdale C.B.

The notifications of acute poliomyelitis were 4 fewer for paralytic cases and 2 fewer for non-paralytic cases than in the preceding week. Liverpool C.B. with 2 cases was the only administrative area with more than one case.

The largest centres of dysentery were Lancashire 129 (Liverpool C.B. 37, Oldham C.B. 30, Manchester C.B. 25); Norfolk 65 (Norwich C.B. 62); London 56 (Hackney 11, Islington 10); Surrey 42 (Woking U.D. 11); Middlesex 42 (Willesden M.B. 17); Glamorganshire 33 (Cardiff C.B. 28); Southampton County 20 (Portsmouth C.B. 10); Northumberland 20 (Newburn U.D. 13); Yorkshire West Riding 20.

Week Ending March 1

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,506, whooping-cough 2,789, diphtheria 33, measles 6,233, acute pneumonia 1,061, acute poliomyelitis 19, dysentery 647, paratyphoid fever 12, and typhoid fever 4.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 23** (No. 8) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	37	3	21	1	1	43	7	10	1	3
Dysentery	591	56	78	3	1	1,366	112	247	9	
Encephalitis, acute	5	0	0	0		8	1	0	0	
Enteric fever:										
Typhoid	3	0	0	1	3	5	2	0	0	2
Paratyphoid	6	0	1 (B)	0		13	0	0	0	
Food-poisoning	85	21		0		119	15		1	
Infective enteritis or diarrhoea under 2 years				10	13				15	18
Measles*	5,734	123	483	152	137	27,776	3746	195	63	64
Meningococcal infection	45	5	25	3	5	45	4	19	2	
Ophthalmia neonatorum	40	2	13	1		32	2	15	0	
Pneumonia†	1,143	50	478	20	3	1,656	81	269	13	137
Poliomyelitis, acute:										
Paralytic	9	1	1	1		16	1	3	2	
Non-paralytic	5	0				5	0			
Puerperal fever§	218	39	9	2		81	6	10	0	
Scarlet fever	1,613	141	251	18	55	828	43	149	37	70
Tuberculosis:										
Respiratory			161	29				179	29	
Non-respiratory			35	4				30	4	
Whooping-cough	2,648	128	418	103	73	5,928	425	840	40	117

DEATHS in Great Towns	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0		0	0	*1*	0	*0*	0	0
Dysentery	0	0		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0		0		*0*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	14		1	0	1	*18*		*7*	1	0
Influenza	29	6	9	1	0	*317*	22	*11*	6	18
Measles		0	1	0	0		1	*0*	0	0
Meningococcal infection		0					0	*1*		
Pneumonia	368	57		18	20	*434*	62		11	10
Poliomyelitis, acute	0	0			0	*2*	0			0
Scarlet fever		0		0	0		0	*0*	0	0
Tuberculosis:										
Respiratory	176	24	30	4	14	*200*	33	*28*	10	11
Non-respiratory		3	5	1	4		1	*5*	2	3
Whooping-cough	4	0		2	1	*14*	2	*1*	0	1
Deaths 0–1 year	296	32	43	23	13	*289*	28	*50*	5	30
Deaths (excluding stillbirths)	6,856	967	796	162	202	*7,009*	1007	*799*	177	276
LIVE BIRTHS	8,101	1249	910	234	375	*7,593*	1242	*941*	237	358
STILLBIRTHS	231	30	28			*222*	26	*26*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Medical Society of London.—Mr. A. C. Palmer presided over the 172nd anniversary dinner of the Medical Society of London at Claridge's on March 6. After the loyal toasts and the customary silent toast to John Coakley Lettsom the health of the society was proposed by Lord Radcliffe. Expressing his pleasure to be dining with the society, he said that in reading the life of Lettsom he had been interested to see the emphasis Lettsom placed upon the pleasures of dining—"tea, punch, and fine liqueurs came in their turn." Lord Radcliffe said he enjoyed speaking to members of a kindred profession, for this made for informality. But the learned professions were a dying industry. The ideals of a factory civilization were creeping in, clocking-in and clocking-out being the rule of the day. People might come to forget what was the meaning of these learned professions, requiring a long apprenticeship in their skill and a background of knowledge studied as a fruitful source for the pursuits of the calling. The learned professions were institutions with a long history behind them. Their traditions and codes built up over the years gave them, the members of the profession, strength. With the help of its codes and standards a member of a learned profession had the guidance necessary to balance, as he always had to, the interests of the patient or client and the interests of society. These were virtues which you could destroy but not re-create. Lord Radcliffe ended by giving an enchanting description of Zoffany's picture of Lettsom, the founder of the society. Zoffany, added Lord Radcliffe, was the perfect painter of the conversation piece.

In reply the president said he could recall no time in which there had been such a flowering of new discoveries in medicine, and it was the function of the society to discuss these. Somewhere beyond the future, he said, there lay perhaps the discovery of the ingredients of synthetic man. He ended by paying a tribute to the honorary secretaries and the treasurer of the society and to Sir Hugh Lett, who, he said, had taught him the principles of surgery. The health of the visitors was proposed in a witty and apt speech by Dr. Wilfrid Oakley, who, admitting that in a moment of weakness he had agreed to propose the toast, said he now understood the fate of the Roman Empire, which at least had had the wisdom to decline before it fell. In welcoming the principal guest of the evening, Lord Radcliffe, he made appreciative reference to his recent Reith lectures on "Power and the State." He reminded those present of one of Sir Hugh Lett's early contributions to surgery, which was a statistical review of a thousand cases of appendicitis, and also of Sir Hugh's accomplishments as a musician. In reply Sir Hugh Lett said that as a registrar at the London Hospital he was encouraged by Treves to collect records of cases of appendicitis, and that was how he came to give his account of the thousand cases. Treves was led to this as a result of a discussion which took place in the Medico-Chirurgical Society. Sir Hugh, in paying a tribute to the society, said that the standard of its lectures and discussions was very high. They had a fine old library, and pervading everything was a friendly and genial atmosphere of its own. Together with Jonathan Hutchinson, junior, he had presented a paper to the society in 1905. Sir Hugh ended with a warm tribute to the president, Mr. A. C. Palmer, whom he recalled as a New Zealander who played rugger for England against Ireland.

Ministry of Health NOT in Whitehall.—Although the Ministry changed its address over eight months ago, four out of every ten letters are still wrongly addressed. This not only causes delay but involves extra work in sorting and re-directing. All correspondence should be addressed to Savile Row, London, W.1.

New Medical Journal at Leeds.—The University of Leeds used to produce a medical magazine which was partly the

organ of the Medical Society and of students, nurses, and auxiliaries. However, it was found that most of the subscribers were qualified doctors, and the magazine has therefore been reborn as the *University of Leeds Medical Journal*, with the support of the Leeds and West Riding Medico-Chirurgical Society, in a form likely to appeal to the graduate and to general practitioners in the region. There will be three issues a year, the first being a symposium: this year on tuberculosis, and in 1953 on emergencies in general practice. It should play a very valuable part in developing that regional enthusiasm in medicine which is so necessary for healthy development and which the present domination by London may impede.

"Ulisse" Prize for 1952.—*Ulisse*, an international cultural magazine, founded in 1949 a prize of one million lire to be awarded annually to the author of a scientific publication produced during the preceding five years. The 1952 prize will be for a work on biochemistry considered in relation to the human organism, with special emphasis on its application to medicine. Works published during the last five years in Europe (in any European language) will be considered, and entries should be submitted to the *Rivista Ulisse*, Corso d'Italia, 43, Rome, not later than April 15.

Ulster Paediatric Society.—A joint meeting of the society with the British Medical Association (Northern Ireland Branch) was held in the Whitla Medical Institute, Belfast, on February 7, when Mr. James Crooks spoke on sinusitis in childhood, and illustrated his talk with a film showing the out-patient treatment. At a further meeting at the Royal Maternity Hospital, Belfast, on February 19, Dr. Mary Cross spoke on retrolental fibroplasia.

Emergency Bed Service: Applications and Admissions.—During the seven days ending March 10 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 1,176, of whom 87.15% were admitted.

COMING EVENTS

Cancellation.—The postgraduate course in venereology organized by the Institute of Urology announced in the *Journal* of March 8 (p. 555) has had to be postponed.

Medical Association for the Prevention of War.—The inaugural meeting of the London and Home Counties branch will be held at 8 p.m. on Thursday, March 20, in the Small Meeting Hall, Friends House, Euston Road, N.W.1. Dr. E. H. S. Burhop will speak on atomic physics in the cause of peace. All members of the medical profession are invited. The meeting is in no way under the auspices of the Society of Friends. A short business session will precede the talk to establish a permanent committee. Nominations for members are invited and should be sent to Dr. Antony Ryle, 28, Bartholomew Road, N.W.5.

Postgraduate Radiology Course.—The Faculty of Radiologists is holding a week-end course for postgraduates on March 22 and 23 at the Royal College of Surgeons, Lincoln's Inn Fields, W.C.2. The morning sessions will be devoted to diagnostic radiology and the afternoons to radiotherapy. Details may be had from the dean of the Faculty, 45, Lincoln's Inn Fields, W.C.2.

Week-end Course on Rheumatism.—The Empire Rheumatism Council will hold its spring week-end course for postgraduates at the Arthur Stanley Institute, Middlesex Hospital (Peto Place, N.W.1), on April 25 and 26. The fee for the course will be two guineas, and the number of entries is limited to 60; application should be made to the general secretary, Empire Rheumatism Council, Tavistock House (N.), W.C.1, at least one week before the course.

8th International Surgical Congress.—The International College of Surgeons will hold its next congress in Madrid from May 19 to 24. Full details may be obtained from the secretary of the congress, Instituto Nacional de Medicina y Seguridad del Trabajo, Facultad de Medicina, Pabellón 8, Ciudad Universitaria, Madrid.

Harveian Oration.—The Oration of the Harveian Society of London will be delivered by Sir John McNee at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C., on Thursday, March 20, at 8.15 p.m. His subject is "Infective Hepatitis: A Problem of World Health."

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Friday, March 14

SOCIETY OF PUBLIC ANALYSTS: BIOLOGICAL METHODS GROUP.—At Chemical Society, Burlington House, Piccadilly, London, W., 6.30 p.m., "*The Assay of Coagulants and Anticoagulants*," papers by Dr. Rosemary Biggs, and Mr. V. J. Birkinshaw and Mr. K. L. Smith. A discussion will follow.

Monday, March 17

HUNTERIAN SOCIETY.—At Talbot Restaurant, 64, London Wall, E.C., 7 for 7.30 p.m., dinner-meeting: "*The Contribution of Surgery to Neurology*," discussion to be opened by Professor Lambert Rogers and Dr. J. Spillane.

Tuesday, March 18

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., 5.30 p.m., "*Physical Techniques in the Medical Applications of Ionizing Radiations*," by Professor W. V. Mayneord.

EUGENICS SOCIETY.—At Royal Society, Burlington House, Piccadilly, London, W., 5.30 p.m., "*The Stability of Marriage*," by Mr. A. J. Brayshaw, B.A. All interested are invited.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., "*Parasitic Diseases*," by Dr. S. Thomson.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—5 p.m., "*Transplantation of Homologous Tissue and its Surgical Applications*," Hunterian Lecture by Professor M. F. A. Woodruff.

SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, Wandsworth Common, London, S.W., 8.30 p.m., "*Modern Skins and Modern Drugs*," by Dr. W. J. O'Donovan.

Wednesday, March 19

BIRMINGHAM MEDICAL INSTITUTE: MIDLAND MEDICAL SOCIETY.—At 154, Great Charles Street, Birmingham, "*Diagnosis and Treatment of Ulcerative Colitis*," by Professor T. L. Hardy and Mr. B. N. Brooke.

FACULTY OF ANAESTHETISTS: ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—4 p.m., annual general meeting. 5 p.m., "*Antecedents of Early Anaesthetic Apparatus*," Joseph Clover Lecture by Professor R. R. Macintosh.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., "*Immunology in Relation to Dermatology*," by Dr. J. O. Oliver.

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, Endell Street, London, W.C., 4.30 for 5 p.m., "*Enuresis*," by Mr. A. R. C. Higham.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, London, W.—3.30 p.m., "*First Aid in the Home*," by Dr. R. W. Barr-Brown.

Thursday, March 20

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, London, W.—8 p.m., "*The Sieve in Radiotherapy*," by Dr. B. Jolles.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., 5.30 p.m., "*Biological Effects of Radiation*," by Dr. J. F. Loutit.

EDINBURGH CLINICAL CLUB.—At B.M.A. Rooms, 7, Drumsheugh Gardens, Edinburgh, 8 p.m., "*The Psychological Approach in General Practice*," by Dr. A. Murray Marr.

●INSTITUTE OF CHILD HEALTH, Hospital for Sick Children, Great Ormond Street, London, W.C.—5 p.m., "*Genito-urinary Surgery*," by Mr. T. Twistington Higgins.

LIVERPOOL MEDICAL INSTITUTION.—At County Hospital, Whiston, nr. Prescot, Lancs, 2.30 p.m., afternoon clinical demonstration.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—5 p.m., "*Hyperplasia and Metaplasia in Synovial Membrane*," Hunterian Lecture by Professor G. R. Fisk.

ROYAL SANITARY INSTITUTE.—At Town Hall, Tavistock, 10 a.m., Papers: "*Rural Planning with Particular Reference to National Parks*," by Mr. Geoffrey Clark, L.R.I.B.A., M.T.P.I.; "*The Incidence of Infantile Paralysis in a Rural Area During the Last Fifteen Years*," by Dr. E. D. Allen Price. Afternoon visits.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At Royal Army Medical College, Millbank, London, S.W., 7.30 p.m., laboratory meeting.

Friday, March 21

BIOCHEMICAL SOCIETY.—At National Institute for Medical Research, Mill Hill, London, N.W., 10.30 a.m., annual general meeting. Scientific papers will be read.

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, London, W.—5 p.m., medical members' meeting; 6.30 p.m., "*The Schmidt Camera—Its Possibilities and Limitations in Photofluorography*," by Mr. W. A. Langmead, M.Sc.

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C., 4 p.m., Radiotherapy Section Meeting. "*The Application of Plastic Surgery to Radiotherapy*," by Mr. J. Scott Tough.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., clinical demonstration by Dr. E. J. Moynahan.

MANCHESTER UNIVERSITY.—5 p.m., "*Women in the Professions*," Margaret Ashton Memorial Lecture by Miss Rose Heilbron, Q.C.

MIDDLESEX COUNTY MEDICAL SOCIETY.—At Hillingdon Hospital, nr. Uxbridge, Middlesex, 3 p.m., general meeting; demonstration of cases, etc.; 4.45 p.m., "*Pharyngeal Diverticulum; Aetiology, Diagnosis, and Treatment*," paper by Mr. F. Boyes Korkis.

●ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—5 p.m., "*Nocturia—A Defeat in the Battle Against Gravity*," first Thomas Young Lecture by Professor J. G. G. Borst (Amsterdam).

SOCIETY OF CHEMICAL INDUSTRY: FINE CHEMICALS GROUP.—At King's College, Strand, London, W.C., 7 p.m., annual general meeting; 7.30 p.m., "*The Physico-chemical Aspects of Drug Administration*," by Dr. N. Evers.

Saturday, March 22

NUTRITION SOCIETY.—At Physiology Lecture Theatre, Manchester University, 10.30 a.m., "*Diet in Relation to Renal and Cardiovascular Disease*," speakers, Dr. J. F. Wilkinson, M.Sc., Ph.D. (chairman), Professor R. Platt, M.Sc., Dr. D. A. K. Black, Dr. Honor Roscoe, Ph.D., Dr. A. M. Jones, M.Sc., Professor A. M. Boyd, M.Sc., and Dr. A. H. Ratcliffe, D.Sc. A discussion will follow.

APPOINTMENTS

The Queen has appointed Dr. Yeo Kok Cheang to be an Official Member of the Legislative Council of Hong Kong.

BARCLAY, GORDON ANDREW, M.B., B.Chir., F.R.C.S., Part-time Consultant Surgeon, St. Andrew's Hospital, Devons Road, London, E.

BIRCHALL, JOHN CRAVEN, M.B., Ch.B., D.P.H., Deputy Medical Officer of Health and Deputy School Medical Officer, County Borough of Croydon.

BOYLE, GERALD F., M.B., Ch.B., D.P.H., Assistant Medical Officer of Health, County of Stirlingshire.

HAWKSLEY, MRS. MARGARET, M.B., B.S., D.A., Consultant Anaesthetist, Hospital for Sick Children, Great Ormond Street, London, W.C.

HENDERSON, ALEXANDER, M.B., Ch.B., D.P.H., Medical Officer of Health, County of Kincardine, from October 1.

SANGSTER, A. J., M.B., Ch.B., D.M.R., Assistant Radiologist, Northern Regional Hospital Board (Scotland).

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—*Consultant Surgeon to Plymouth Clinical Area*, H. D. S. Vellacott, M.B., B.Chir., F.R.C.S. *Consultant Physician to Plymouth Clinical Area*, H. A. W. Forbes, B.M., B.Ch., M.R.C.P. *Consultant Pathologist to Plymouth Clinical Area*, G. A. Cary Lynch, M.D., D.P.H.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Black.—On February 18, 1952, in Birmingham, to Dr. Margaret Black, wife of Dr. Alan Black, a son.

Patey.—On March 4, 1952, at Paignton Hospital, Devon, to Jean Patey, M.B., F.R.C.S.Ed (formerly Mason), wife of John Patey, a sister for Robert and Johnny.

Rees.—On February 28, 1952, at Moorlands Maternity Home, Dewsbury, Yorks, to Marie, wife of Dr. D. F. Rees, twin sisters for Patricia.

Shribman.—On February 25, 1952, at Victoria Hospital, Barnet, Herts, to Hazel, wife of Dr. Irvine Shribman, a son—Jonathan Howard.

DEATHS

Bull.—On February 29, 1952, at Bedford, George Coulson Robins Bull, M.B., F.R.C.S., L.D.S., aged 94.

Findlay.—On February 21, 1952, John Findlay, M.B.E., M.D., of 14, Chada Avenue, Gillingham, Kent, formerly of Peterhead.

Green.—On February 25, 1952, in a London nursing-home, Frederick James Green, M.C., M.D. late of 9, Old Burlington Street, London, W., aged 83.

Murphy.—On February 23, 1952, Lionel Caldbeck Esmonde Murphy, L.R.C.P.&S.I. & L.M., aged 74.

Power.—On February 28, 1952, in London, Michael Patrick Power, O.B.E., M.C., L.R.C.P.&S.Ed., L.R.F.P.S., Colonel, late R.A.M.C., of the Naval and Military Club.

Preston.—On February 23, 1952, at his home, Redlands, Mansfield Woodhouse, Notts, Harold Braycott Preston, L.M.S.S.A.

Skevington.—On February 29, 1952, at Belmont, 15, York Road, Windsor, Berks, Sir Joseph Oliver Skevington, K.C.V.O., F.R.C.S., aged 79.

Walsh.—On February 24, 1952, in London, John Walsh, M.B., B.Ch., Major, R.A.M.C., retired, late of Classis, Ballincollig, Co. Cork, Eire.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Visiting Children in Hospital

Q.—*Is it true that there is good evidence to show that serious psychological harm may occur to young children in hospital, especially if they are not visited regularly by their parents? If so, can the policy of denying such visits to the patients in fever hospitals still be justified?*

A.—There are really several parts to this question, of which the first is whether separation from their parents causes psychological harm to young children. It is quite evident that it does upset some children, and they may show this at the time or on their return home. The second part of the question is whether the harm done is serious and long-lasting; there is fairly good evidence that this may be so, but by no means in the majority of infants. It is probable that serious harm is more likely to occur when separation is prolonged and in infants round about the small toddler age. It is more likely also where there is already some emotional disturbance in the home, or lack of a stable background. Thirdly, does frequent visiting diminish this risk? There is little doubt that frequent visiting increases the happiness of most children in hospital, so that it may be expected to diminish any harm that may come from separation; the value of weekly or less frequent visits must be more doubtful.

The final question is whether the possible harm done by separation outweighs the objections to visiting. The latter include such things as the increase in the strain on the nursing and cleaning staff caused by frequent visitors, and the risks of cross-infection where wards are open and the age groups mixed and where perhaps there is already some overcrowding. The effect on children who cannot be visited and the effect of the extra travelling on parents and transport must also be considered. In a fever hospital the question of the spread of infection by visitors and the maintenance of barrier nursing require consideration before visiting can be encouraged. It seems reasonable to say that frequent visiting seems good in itself and should be permitted, at least on an experimental scale, wherever conditions make it possible. It might be found impracticable in some hospitals, and it would then have to be stopped. It must not be forgotten that, as life in hospital can never be right for children, the aim must always be to return them home as soon as possible, and visiting must remain a secondary consideration to other medical and nursing requirements.

Dangerous Hypotension after Anaesthesia

Q.—*After a general anaesthetic, when the mask is removed from the patient's face there is a marked fall of blood pressure due to the anaesthetic and independent of the surgical manipulation. What is the cause of this fall of blood pressure? How may it be prevented?*

A.—The following are a few of the reasons why the blood pressure sometimes falls when the anaesthetic and the operation come to an end: (1) Stimuli from the operation field may have been reflexly keeping up the blood pressure. (2) The anaesthetic itself, particularly ether, and probably others too, may reflexly raise the blood pressure by stimulating nerve endings in the respiratory tract or the circulatory centre. (3) Carbon dioxide accumulation during the operation may keep the blood pressure up. This is found commonly when the semi-closed method is used. With gas-flow as low as 6 to 8 litres per minute there is

almost invariably some degree of re-breathing. In closed-circuit anaesthesia unsuspected partial exhaustion of the soda lime may occur. (4) With anaesthetics which depress the respiration, such as cyclopropane and thiopentone, or when relaxants are used, the ventilation may be insufficient for adequate carbon dioxide clearance and carbon dioxide accumulation occurs. (5) The volume of dead space may unsuspectedly be sufficiently large to cause some carbon dioxide accumulation.

All these causes cease to operate when the mask is taken off the face, and sometimes the resultant drop in blood pressure may be sufficiently severe to give the appearance of shock. The phenomenon may to a large extent be prevented by careful attention to adequate ventilation and carbon dioxide clearance throughout the operation, and to the correction of any chemical or physical factor in the apparatus which might hinder this.

Neonatal Priapism

Q.—*An infant delivered by caesarean section had a constant priapism for the first 14 days of life; the priapism is now intermittent. The baby in other respects appears quite normal, except that it needs circumcision. What is the likely cause of the priapism? What investigations, if any, are indicated? What are the prognosis and treatment?*

A.—Priapism is a not infrequent occurrence in the newborn period and is usually without significance. It occurs independently of the method of delivery, and is most unlikely to be an indication of spinal cord damage or local trauma in the case quoted. "Constant" priapism is said to have been present for 14 days. This is unusual, but a highly active reflex from the skin could quite easily cause an erection each time the infant was examined.

No investigations are indicated: no treatment is necessary: the prognosis is good.

Home-made Hair Oil

Q.—*Can you suggest an inexpensive prescription for a hair "fixative" for men?*

A.—A satisfactory preparation for those who prefer a non-greasy hair fixative is as follows: Powdered tragacanth 1.2%, alcohol 15%, glycerin 10%, water to 100%, perfume and preservative as required. A suitable preservative is 0.1% chlorocresol or the "solution for eye drops" of the *National Formulary*. For those who like a greasy preparation 10% of arachis or olive oil may be added to this formula. Further information may be obtained from *Modern Cosmeticology*, by Harry (Chapman and Hall, 1944).

Does Agene Destroy Vitamins in Flour?

Q.—*Has the agene process any effect on the vitamin content of flour, whether the vitamins are derived from the cereals themselves or are supplements?*

A.—The most obvious effect of agene (NCl_3) on flour is to reduce the yellow carotenoid pigments naturally present to about one-third of the original level, but as these are mostly xanthophyll, which is inactive as pro-vitamin A, this loss is of little importance from a nutritional standpoint. In the vitamin-B group there is probably some loss of riboflavin, but most of the other members are more stable. Probably vitamin E is reduced. The question of the vulnerability of added vitamins is difficult to answer. In Britain flour is not fortified with vitamins, while in the U.S.A., where vitamins are sometimes added, agene has been banned. However, it should be practicable to add unstable vitamins after the inactivation of the improver by the bulk of the flour. The action of agenized flour in producing "hysteria" in dogs, of course, is due to the formation of a toxic substance rather than to the destruction of vitamins.

Endocrine Therapy of Delirium Tremens

Q.—*I have heard it said that adrenocorticotrophic hormone (A.C.T.H.) and cortisone can cut short an attack of delirium tremens. Is this true? If it is, how should the treatment be given?*

A.—A considerable amount of evidence has accumulated to suggest that A.C.T.H. and cortisone may have a dramatic effect in cutting short an attack of delirium tremens. Both drugs will have to be used with great caution in such a condition, however, as delirium tremens is not infrequently associated with cardiac embarrassment which will be exacerbated by such therapy. Further, delirium tremens may be precipitated, as it often is, by an infective illness, and again acute infections may be aggravated by cortisone and A.C.T.H. In the treatment of delirium tremens A.C.T.H. is probably preferable to cortisone. A suitable dose would be 25 mg. six-hourly.

NOTES AND COMMENTS

Boy or Girl?—Mr. D. INNES WILLIAMS (London) writes: Many of your readers will have been interested in the case of the infant with an absence of the scrotum ("Any Questions?" February 9, p. 340). It is disappointing, however, to find that your questioner is advised to embark on endocrine therapy without any attempt to establish the diagnosis by ordinary clinical investigation. A simple rectal examination, to those accustomed to the procedure in infants, is capable of giving a great deal of information regarding the anatomy of genital passages: moreover, with instruments now available, urethroscopy is now possible at a very early age, and is of the greatest assistance in determining the sex in doubtful cases. The latter point is dealt with fully in a paper of mine now awaiting publication.

Emetine and Scorpion Stings.—Dr. C. HOLLINS (Dorchester) writes: I agree that intramuscular emetine is useless for scorpion stings ("Any Questions?" February 16, p. 396), but emetine injected at the site of the sting is an excellent remedy. I once did a controlled experiment (with the patient's consent) by first injecting saline at the site of the scorpion sting; the pain was aggravated. I then injected emetine and the pain was immediately relieved. The sting was on the foot, and there was already considerable pain in the inguinal glands. This pain disappeared a few minutes after the pain at the site of the sting. I have not noticed this effect with procaine, but pain in the regional lymph glands is unusual anyway.

Dr. H. ABDALLA (London), after stating that emetine was used in the Sudan for treating scorpion stings, writes: Injection of 1 gr. (65 mg.) emetine hydrochloride intramuscularly, or the local injection into the sting site of much smaller amounts (which may be as small as 1/16 gr. (4 mg.)) diluted with distilled water, causes immediate cessation of pain and all other symptoms of the sting. It is superior to local analgesic infiltration in that the latter has to be repeated in from 15 minutes to two hours and is of no use once the symptoms of shock have been established. As regards antivenin treatment, factors of supply, storage, climate, etc., continue to stand against its general adoption throughout scorpion-infested areas.

Notification of Pemphigus Neonatorum.—A MEDICAL OFFICER OF HEALTH has written to point out that the councils of some districts have under Section 147 of the Public Health Act, 1936, declared pemphigus neonatorum ("Any Questions?" February 23, p. 448) to be notifiable in their areas.

Correction.—Dr. CHARLES NEWMAN (dean of the Postgraduate Medical School of London) asks us to point out that the British Postgraduate Medical School is now termed a Federation, of which his school is a constituent, and that it is the Federation as a whole, and not his school, which is discussed in our annotation (March 1, p. 479).

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